Santodonato, L., et al., Gene Therapy 4:1246-1255 (1997); and Zhang, J.-F. et al., Cancer Gene Therapy 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells which are engineered are arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

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As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

In one embodiment, the polynucleotide of the present invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotide of the present invention can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

Any strong promoter known to those skilled in the art can be used for driving the expression of the polynucleotide sequence. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the ApoAI promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-

245

actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the polynucleotide of the present invention.

Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

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The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. In vivo muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked nucleic acid sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues,

246

throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

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The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

In certain embodiments, the polynucleotide constructs are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA (1989) 86:6077-6081, which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem. (1990) 265:10189-10192, which is herein incorporated by reference), in functional form.

Cationic liposomes are readily available. For example, N[1-2,3-dioleyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y. (See, also, Felgner et al., Proc. Natl Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication No. WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., P. Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl, choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphoshatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at 15EC. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., Methods of Immunology (1983), 101:512-527, which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated. SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to

the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include Ca²⁺-EDTA chelation (Papahadjopoulos et al., Biochim. Biophys. Acta (1975) 394:483; Wilson et al., Cell (1979) 17:77); ether injection (Deamer, D. and Bangham, A., Biochim. Biophys. Acta (1976) 443:629; Ostro et al., Biochem. Biophys. Res. Commun. (1977) 76:836; Fraley et al., Proc. Natl. Acad. Sci. USA (1979) 76:3348); detergent dialysis (Enoch, H. and Strittmatter, P., Proc. Natl. Acad. Sci. USA (1979) 76:145); and reverse-phase evaporation (REV) (Fraley et al., J. Biol. Chem. (1980) 255:10431; Szoka, F. and Papahadjopoulos, D., Proc. Natl. Acad. Sci. USA (1978) 75:145; Schaefer-Ridder et al., Science (1982) 215:166), which are herein incorporated by reference.

Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the ration will be about 1:3. Still more preferably, the ratio will be about 1:1.

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U.S. Patent No. 5,676,954 (which is herein incorporated by reference) reports on the injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide methods for delivering DNA-cationic lipid complexes to mammals.

In certain embodiments, cells are engineered, ex vivo or in vivo, using a retroviral particle containing RNA which comprises a sequence encoding a polypeptide of the present invention. Retroviruses from which the retroviral plasmid vectors may be derived include, but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, Human Gene Therapy 1:5-14 (1990), which is incorporated herein by reference in its entirety. The vector

249

may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and CaPO₄ precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

The producer cell line generates infectious retroviral vector particles which include polynucleotide encoding a polypeptide of the present invention. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either in vitro or in vivo. The transduced eukaryotic cells will express a polypeptide of the present invention.

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In certain other embodiments, cells are engineered, ex vivo or in vivo, with polynucleotide contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses a polypeptide of the present invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have been used as live enteric vaccines for many years with an excellent safety profile (Schwartz, A. R. et al. (1974) Am. Rev. Respir. Dis.109:233-238). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld, M. A. et al. (1991) Science 252:431-434; Rosenfeld et al., (1992) Cell 68:143-155). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green, M. et al. (1979) Proc. Natl. Acad. Sci. USA 76:6606).

Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, Curr. Opin. Genet. Devel. 3:499-503 (1993); Rosenfeld et al., Cell 68:143-155 (1992); Engelhardt et al., Human Genet. Ther. 4:759-769 (1993); Yang et al., Nature Genet. 7:362-369 (1994); Wilson et al., Nature 365:691-692 (1993); and U.S. Patent No. 5,652,224, which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the E1 region of adenovirus and constitutively express Ela and Elb, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to Ad2, other varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

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Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of infecting cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: Ela, Elb, E3, E4, E2a, or L1 through L5.

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In certain other embodiments, the cells are engineered, ex vivo or in vivo, using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyczka, N., Curr. Topics in Microbiol. Immunol. 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S. Patent Nos. 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell integration. The polynucleotide construct is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus, using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses. Once the packaging cells are transfected and infected, they will produce infectious AAV viral particles which contain the polynucleotide construct. These viral particles are then used to transduce eukaryotic cells, either ex vivo or in vivo. The transduced cells will contain the polynucleotide construct integrated into its genome, and will express a polypeptide of the invention.

Another method of gene therapy involves operably associating heterologous control regions and endogenous polynucleotide sequences (e.g. encoding a polypeptide of the present invention) via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc.

Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

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The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can be delivered by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

Preferably, the polynucleotide encoding a polypeptide of the present invention contains a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5' end of the coding region. The signal sequence may be homologous or heterologous to the polynucleotide of interest and may be homologous or heterologous to the

cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection, systemic injection, catheter infusion, biolistic injectors, particle accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppositorial solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium phosphate-precipitated plasmid into rat liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers (Kaneda et al., Science 243:375 (1989)).

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A preferred method of local administration is by direct injection. Preferably, a recombinant molecule of the present invention complexed with a delivery vehicle is administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a patient can undergo surgery and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue inside the wound.

Therapeutic compositions useful in systemic administration, include recombinant molecules of the present invention complexed to a targeted delivery vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a particular site.

Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be performed using methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad. Sci. USA 189:11277-11281, 1992, which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the gut of an animal. Examples of such

carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian.

Therapeutic compositions of the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly preferred.

15 Biological Activities

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Polynucleotides or polypeptides, or agonists or antagonists of the present invention, can be used in assays to test for one or more biological activities. If these polynucleotides or polypeptides, or agonists or antagonists of the present invention, do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides, and agonists or antagonists could be used to treat the associated disease.

Immune Activity

A polypeptide or polynucleotide, or agonists or antagonists of the present invention may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, polynucleotides or polypeptides, or

agonists or antagonists of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

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Polynucleotides or polypeptides, or agonists or antagonists of the present invention may be useful in treating or detecting deficiencies or disorders of hematopoietic cells. Polynucleotides or polypeptides, or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to: blood protein disorders (e.g. agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency, Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.

Moreover, polynucleotides or polypeptides, or agonists or antagonists of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, polynucleotides or polypeptides, or agonists or antagonists of the present invention could be used to treat blood coagulation disorders (e.g., afibrinogenemia, factor deficiencies), blood platelet disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, polynucleotides or polypeptides, or agonists or antagonists of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment of heart attacks (infarction), strokes, or scarring.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention may also be useful in treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of polynucleotides or polypeptides, or agonists or antagonists of the present invention that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

Examples of autoimmune disorders that can be treated or detected include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitis, and autoimmune inflammatory eye disease.

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Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of polynucleotides or polypeptides, or agonists or antagonists of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, polynucleotides or polypeptides, or agonists or antagonists of the present invention may also be used to modulate inflammation. For example, polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including chronic prostatitis, granulomatous prostatitis and malacoplakia, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.)

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Hyperproliferative Disorders

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Polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used to treat or detect hyperproliferative disorders, including neoplasms. Polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, Polynucleotides or polypeptides, or agonists or antagonists of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by Polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to neoplasms located in the: colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstron's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

One preferred embodiment utilizes polynucleotides of the present invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

Thus, the present invention provides a method for treating cell proliferative disorders by inserting into an abnormally proliferating cell a polynucleotide of the present invention, wherein said polynucleotide represses said expression.

Another embodiment of the present invention provides a method of treating cellproliferative disorders in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells. In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the poynucleotides of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferrably an adenoviral vector (See G J. Nabel, et. al., PNAS 1999 96: 324-326, which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present invention inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e. magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e. to increase, decrease, or inhibit expression of the present invention) based upon said external stimulus.

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Polynucleotides of the present invention may be useful in repressing expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes" is intended the suppression of the transcription of the gene, the degradation of the gene transcript (premessage RNA), the inhibition of splicing, the destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the normal function of the protein.

For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in the art including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any other method described throughout the specification. The polynucleotide of the present invention may be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature 320:275 (1986); Wilson, et al., Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403)

258

(1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references are exemplary only and are hereby incorporated by reference. In order to specifically deliver or transfect cells which are abnormally proliferating and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes needed for its life cycle. Utilizing such a retroviral delivery system for polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-dividing normal cells.

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The polynucleotides of the present invention may be delivered directly to cell proliferative disorder/disease sites in internal organs, body cavities and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The polynucleotides of the present invention may also be administered to disease sites at the time of surgical intervention.

By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the polynucleotide of the present invention simultaneously to the same site. By "biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells. The biologically inhibitory dose may be determined by assessing the effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell growth in tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

The present invention is further directed to antibody-based therapies which involve administering of anti-polypeptides and anti-polynucleotide antibodies to a mammalian, preferably human, patient for treating one or more of the described disorders. Methods for producing anti-polypeptides and anti-polynucleotide antibodies polyclonal and monoclonal

antibodies are described in detail elsewhere herein. Such antibodies may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

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In particular, the antibodies, fragments and derivatives of the present invention are useful for treating a subject having or developing cell proliferative and/or differentiation disorders as described herein. Such treatment comprises administering a single or multiple doses of the antibody, or a fragment, derivative, or a conjugate thereof.

The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors, for example., which serve to increase the number or activity of effector cells which interact with the antibodies.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragements thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides, including fragements thereof. Preferred binding affinities include those with a dissociation constant or Kd less than 5X10⁻⁶M, 10⁻⁶M, 5X10⁻⁷M, 10⁻⁷M, 5X10⁻⁸M, 10⁻⁸M, 5X10⁻¹⁹M, 5X10⁻¹⁰M, 10⁻¹⁰M, 5X10⁻¹¹M, 10⁻¹¹M, 5X10⁻¹²M, 10⁻¹²M, 5X10⁻¹³M, 10⁻¹³M, 5X10⁻¹⁴M, 10⁻¹⁴M, 5X10⁻¹⁵M, and 10⁻¹⁵M.

Moreover, polypeptides of the present invention are useful in inhibiting the angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in combination with other polypeptides directly or indirectly, as described elsewhere herein. In a most preferred embodiment, said anti-angiogenesis effect may be achieved indirectly, for example, through the inhibition of hematopoietic, tumor-specific cells, such as tumor-associated macrophages (See Joseph IB, et al. J Natl Cancer Inst, 90(21):1648-53 (1998),

which is hereby incorporated by reference). Antibodies directed to polypeptides or polynucleotides of the present invention may also result in inhibition of angiogenesis directly, or indirectly (See Witte L, et al., Cancer Metastasis Rev. 17(2):155-61 (1998), which is hereby incorporated by reference)).

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Polypeptides, including protein fusions, of the present invention, or fragments thereof may be useful in inhibiting proliferative cells or tissues through the induction of apoptosis. Said polypeptides may act either directly, or indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1), TNF-receptor-related apoptosis-mediated protein (TRAMP) and TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (See Schulze-Osthoff K, et.al., Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by reference). Moreover, in another preferred embodiment of the present invention, said polypeptides may induce apoptosis through other mechanisms, such as in the activation of other proteins which will activate apoptosis, or through stimulating the expression of said proteins, either alone or in combination with small molecule drugs or adjuviants, such as apoptonin, galectins, thioredoxins, antiinflammatory proteins (See for example, Mutat Res 400(1-2):447-55 (1998), Med Hypotheses.50(5):423-33 (1998), Chem Biol Interact. Apr 24;111-112:23-34 (1998), J Mol Med.76(6):402-12 (1998), Int J Tissue React:20(1):3-15 (1998), which are all hereby incorporated by reference).

Polypeptides, including protein fusions to, or fragments thereof, of the present invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering polypeptides, or antibodies directed to said polypeptides as described elsewere herein, or indirectly, such as activating the expression of proteins known to inhibit metastasis, for example alpha 4 integrins, (See, e.g., Curr Top Microbiol Immunol 1998;231:125-41, which is hereby incorporated by reference). Such thereapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

In another embodiment, the invention provides a method of delivering compositions containing the polypeptides of the invention (e.g., compositions containing polypeptides or polypeptide antibodes associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs) to targeted cells expressing the polypeptide of the present invention. Polypeptides or polypeptide antibodes of the invention may be associated with with

261

heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. Polypeptides, protein fusions to, or fragments thereof, of the present invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the polypeptides of the present invention 'vaccinated' the immune response to respond to proliferative antigens and immunogens, or indirectly, such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and immunogens.

10 Cardiovascular Disorders

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Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat cardiovascular disorders, including peripheral artery disease, such as limb ischemia.

Cardiovascular disorders include cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, trilogy of Fallot, ventricular heart septal defects.

Cardiovascular disorders also include heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

262

Arrhythmias include sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole. Adams-Stokes Syndrome, bundle-branch block, sinoatrial block, long QT syndrome, parasystole. Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

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Heart valve disease include aortic valve insufficiency, aortic valve stenosis, hear murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, and tricuspid valve stenosis.

Myocardial diseases include alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular stenosis, pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial reperfusion injury, and myocarditis.

Myocardial ischemias include coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial infarction and myocardial stunning.

Cardiovascular diseases also include vascular diseases such as aneurysms, angiodysplasia, angiomatosis, bacillary angiomatosis, Hippel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, atacia telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

263

Aneurysms include dissecting aneurysms, false aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

Arterial occlusive diseases include arteriosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery occlusion, and thromboangiitis obliterans.

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Cerebrovascular disorders include carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subaraxhnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

Embolisms include air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromoboembolisms. Thrombosis include coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

Ischemia includes cerebral ischemia, ischemic colitis, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, are especially effective for the treatment of critical limb ischemia and coronary disease.

Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppositorial solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a

264

Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

Anti-Angiogenesis Activity

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The naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastinejad et al., Cell 56:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and nonneoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization including solid tumor growth and metastases, arthritis, some types of eye disorders, and psoriasis. See, e.g., reviews by Moses et al., Biotech. 9:630-634 (1991); Folkman et al., N. Engl. J. Med., 333:1757-1763 (1995); Auerbach et al., J. Microvasc. Res. 29:401-411 (1985); Folkman, Advances in Cancer Research, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203 (1985); Patz, Am. J. Opthalmol. 94:715-743 (1982); and Folkman et al., Science 221:719-725 (1983). In a number of pathological conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun, Science 235:442-447 (1987).

The polynucleotides encoding a polypeptide of the present invention may be administered along with other polynucleotides encoding an angiogenic protein. Examples of angiogenic proteins include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin like growth factor, colony stimulating factor, macrophage colony stimulating factor, and nitric oxide synthase.

The present invention provides for treatment of diseases or disorders associated with neovascularization by administration of the polynucleotides and/or polypeptides of the

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invention, as well as agonists or antagonists of the present invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid tumors, and cancers described herein and otherwise known in the art (for a review of such disorders, see Fishman et al., Medicine, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)). Thus, the present invention provides a method of treating an angiogenesis-related disease and/or disorder, comprising administering to an individual in need thereof a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist of the invention. For example, polynucleotides, polypeptides, antagonists and/or agonists may be utilized in a variety of additional methods in order to therapeutically treat a cancer or tumor. Cancers which may be treated with polynucleotides, polypeptides, antagonists and/or agonists include, but are not limited to solid tumors, including breast, ovarian, prostate, lung, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non- small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, polynucleotides, polypeptides, antagonists and/or agonists may be delivered topically, in order to treat cancers such as skin cancer, head and neck tumors, breast tumors, and Kaposi's sarcoma.

Within yet other aspects, polynucleotides, polypeptides, antagonists and/or agonists may be utilized to treat superficial forms of bladder cancer by, for example, intravesical administration. Polynucleotides, polypeptides, antagonists and/or agonists may be delivered directly into the tumor, or near the tumor site, via injection or a catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

Polynucleotides, polypeptides, antagonists and/or agonists may be useful in treating other disorders, besides cancers, which involve angiogenesis. These disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; artheroscleric plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uvietis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid

266

arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

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For example, within one aspect of the present invention methods are provided for treating hypertrophic scars and keloids, comprising the step of administering a polynucleotide, polypeptide, antagonist and/or agonist of the invention to a hypertrophic scar or keloid.

Within one embodiment of the present invention polynucleotides, polypeptides, antagonists and/or agonists are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of hypertrophic scars and keloids (e.g., burns), and is preferably initiated after the proliferative phase has had time to progress (approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, comeal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental fibroplasia and macular degeneration.

Moreover, Ocular disorders associated with neovascularization which can be treated with the polynucleotides and polypeptides of the present invention (including agonists and/or antagonists) include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g., reviews by Waltman et al., Am. J. Ophthal. 85:704-710 (1978) and Gartner et al., Surv. Ophthal. 22:291-312 (1978).

Thus, within one aspect of the present invention methods are provided for treating neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically effective amount of a compound (as described above) to the cornea, such that the formation

of blood vessels is inhibited. Briefly, the comea is a tissue which normally lacks blood vessels. In certain pathological conditions however, capillaries may extend into the comea from the pericorneal vascular plexus of the limbus. When the comea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may become complete if the comea completely opacitates. A wide variety of disorders can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact lenses.

Within particularly preferred embodiments of the invention, may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The solution or suspension may be prepared in its pure form and administered several times daily. Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer which binds to cornea. Within further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in corneal lesions which are known to have a high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

Within other embodiments, the compounds described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The preferred site of injection may vary with the morphology of the individual lesion, but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbic corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation the material could be injected in the perilimbic cornea interspersed between the corneal lesion and its undesired

268

potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form injections might only be required 2-3 times per year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

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Within another aspect of the present invention, methods are provided for treating neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat early forms of neovascular glaucoma. Within other embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eyes, such that the formation of blood vessels is inhibited.

Within particularly preferred embodiments of the invention, proliferative diabetic retinopathy may be treated by injection into the aqueous humor or the vitreous, in order to increase the local concentration of the polynucleotide, polypeptide, antagonist and/or agonist in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

Within another aspect of the present invention, methods are provided for treating retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. The compound may be administered topically, via intravitreous injection and/or via intraocular implants.

Additionally, disorders which can be treated with the polynucleotides, polypeptides, agonists and/or agonists include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

Moreover, disorders and/or states, which can be treated with be treated with the the polynucleotides, polypeptides, agonists and/or agonists include, but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uvietis, delayed wound healing, endometriosis, vascluogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochele minalia quintosa), ulcers (Helicobacter pylori), Bartonellosis and bacillary angiomatosis.

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In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and fertilization have occurred, thus providing an effective method of birth control, possibly a "morning after" method. Polynucleotides, polypeptides, agonists and/or agonists may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

Polynucleotides, polypeptides, agonists and/or agonists of the present invention may be incorporated into surgical sutures in order to prevent stitch granulomas.

Polynucleotides, polypeptides, agonists and/or agonists may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present invention a compositions (in the form of, for example, a spray or film) may be utilized to coat or spray an area prior to removal of a tumor, in order to isolate normal surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g., in the form of a spray) may be delivered via endoscopic procedures in order to coat tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes which have been coated

270

with anti- angiogenic compositions of the present invention may be utilized in any procedure wherein a surgical mesh might be utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-angiogenic factor.

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Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering a polynucleotide, polypeptide, agonist and/or agonist to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the tumor excision site (e.g., applied by swabbing, brushing or otherwise coating the resection margins of the tumor with the anti-angiogenic compound). Alternatively, the anti-angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

Within one aspect of the present invention, polynucleotides, polypeptides, agonists and/or agonists may be administered to the resection margin of a wide variety of tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one embodiment of the invention, anti-angiogenic compounds may be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

The polynucleotides, polypeptides, agonists and/or agonists of the present invention may also be administered along with other anti-angiogenic factors. Representative examples of other anti-angiogenic factors include: Anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP-PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, 1992); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, 1992); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, 1987); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, 1987); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-

chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316, 1992); Thalidomide; Angostatic steroid; AGM-1470; carboxynaminolmidazole; and metalloproteinase inhibitors such as BB94.

5 Diseases at the Cellular Level

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Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated or detected by polynucleotides or polypeptides, as well as antagonists or agonists of the present invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection. In preferred embodiments, polynucleotides, polypeptides, and/or antagonists of the invention are used to inhibit growth, progression, and/or metasis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's

tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be treated or detected by polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Wound Healing and Epithelial Cell Proliferation

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In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity

wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associted with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote dermal reestablishment subsequent to dermal loss

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Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to increase the adherence of skin grafts to a wound bed and to stimulate re-epithelialization from the wound bed. The following are types of grafts that polynucleotides or polypeptides, agonists or antagonists of the present invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepdermic grafts, avacular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fascia graft, full thickness graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omenpal graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, can be used to promote skin strength and to improve the appearance of aged skin.

It is believed that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intesting, and large intestine. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes, type II pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Polynucleotides or polypeptides, agonists or antagonists of the present invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may have a cytoprotective effect on

the small intestine mucosa. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

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Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to treat gastric and doudenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflamamatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote the resurfacing of the mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with polynucleotides or polypeptides, agonists or antagonists of the present invention, is expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat diseases associate with the under expression.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to prevent and heal damage to the lungs due to various pathological states. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and brochiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of aveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or

polypeptides, agonists or antagonists of the present invention. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary displasia, in premature infants.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetraholoride and other hepatotoxins known in the art).

In addition, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

20 Neurological Diseases

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In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate neurological cell proliferation and/or differentiation. Therefore, polynucleotides, polypeptides, agonists and/or antagonists of the invention may be used to treat and/or detect neurologic diseases. Moreover, polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used as a marker or detector of a particular nervous system disease or disorder.

Examples of neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency, pyruvate dehydrogenase complex deficiency, Wernicke's Encephalopathy, brain edema, brain neoplasms such as

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cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms, supratentorial neoplasms, canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, Machado-Joseph Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as infratentorial neoplasms, diffuse cerebral sclerosis such as encephalitis periaxialis, globoid cell leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis, cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis such as carotid artery thrombosis, sinus thrombosis and Wallenberg's Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar insufficiency, vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache, migraine, dementia such as AIDS Dementia Complex, presenile dementia such as Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as multi-infarct dementia, encephalitis which include encephalitis periaxialis, viral encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome, Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis, encephalomalacia such as periventricular leukomalacia, epilepsy such as generalized epilepsy which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic epilepsy, status epilepticus such as Epilepsia Partialis Continua, Hallervorden-Spatz Syndrome, hydrocephalus such as Dandy-Walker Syndrome and normal pressure hydrocephalus, hypothalamic diseases such as hypothalamic neoplasms, cerebral malaria, narcolepsy which includes cataplexy, bulbar poliomyelitis, cerebri pseudotumor, Rett Syndrome, Reye's Syndrome, thalamic diseases,

cerebral toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous

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system infections such as AIDS Dementia Complex, Brain Abscess, subdural empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna, cerebral malaria, meningitis such as arachnoiditis, aseptic meningtitis such as viral meningtitis which includes lymphocytic choriomeningitis. Bacterial meningtitis which includes Haemophilus Meningtitis, Listeria Meningtitis, Meningococcal Meningtitis such as Waterhouse-Friderichsen Syndrome, Pneumococcal Meningtitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningtitis, subdural effusion, meningoencephalitis such as uvemeningoencephalitic syndrome, myelitis such as transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes bulbar poliomyelitis and postpoliomyelitis syndrome, prion diseases (such as Creutzfeldt-Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie) cerebral toxoplasmosis, central nervous system neoplasms such as brain neoplasms that include cerebellear neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral sceloris which includes adrenoleukodystrophy. encephalitis periaxialis, globoid cell leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, multiple sclerosis, central pontine myelinolysis, transverse myelitis, neuromyelitis optica, Scrapie, Swayback, Chronic Fatigue Syndrome, Visna, High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as amyotonia congenita, amyotrophic lateral sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms such as epidural neoplasms, syringomyelia, Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome, De Lange's Syndrome, Down Syndrome, Gangliosidoses such as gangliosidoses G(M1), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon- Biedl Syndrome, Lesch-Nyhan Syndrome, Maple Syrup Urine Disease, mucolipidosis such as fucosidosis, neuronal ceroidlipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett Syndrome, Rubinstein-Taybi Syndrome, Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as

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holoprosencephaly, neural tube defects such as anencephaly which includes hydrangencephaly, Arnold-Chairi Deformity, encephalocele, meningocele, meningomyelocele, spinal dysraphism such as spina bifida cystica and spina bifida occulta, hereditary motor and sensory neuropathies which include Charcot-Marie Disease, Hereditary optic atrophy, Refsum's Disease, hereditary spastic paraplegia, Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies such as Congenital Analgesia and Familial Dysautonomia, Neurologic manifestations (such as agnosia that include Gerstmann's Syndrome, Amnesia such as retrograde amnesia, apraxia, neurogenic bladder, cataplexy, communicative disorders such as hearing disorders that includes deafness, partial hearing loss, loudness recruitment and tinnitus, language disorders such as aphasia which include agraphia, anomia, broca aphasia, and Wernicke Aphasia, Dyslexia such as Acquired Dyslexia, language development disorders, speech disorders such as aphasia which includes anomia, broca aphasia and Wernicke Aphasia, articulation disorders, communicative disorders such as speech disorders which include dysarthria, echolalia, mutism and stuttering, voice disorders such as aphonia and hoarseness, decerebrate state, delirium, fasciculation, hallucinations, meningism, movement disorders such as angelman syndrome, ataxia, athetosis, chorea, dystonia, hypokinesia, muscle hypotonia, myoclonus, tic, torticollis and tremor, muscle hypertonia such as muscle rigidity such as stiff-man syndrome, muscle spasticity, paralysis such as facial paralysis which includes Herpes Zoster Oticus, Gastroparesis, Hemiplegia, ophthalmoplegia such as diplopia, Duane's Syndrome, Horner's Syndrome, Chronic progressive external ophthalmoplegia such as Kearns Syndrome, Bulbar Paralysis, Tropical Spastic Paraparesis, Paraplegia such as Brown-Sequard Syndrome, quadriplegia, respiratory paralysis and vocal cord paralysis, paresis, phantom limb, taste disorders such as ageusia and dysgeusia, vision disorders such as amblyopia, blindness, color vision defects, diplopia, hemianopsia, scotoma and subnormal vision, sleep disorders such as hypersomnia which includes Kleine-Levin Syndrome, insomnia, and somnambulism, spasm such as trismus, unconsciousness such as coma, persistent vegetative state and syncope and vertigo, neuromuscular diseases such as amyotonia congenita, amyotrophic lateral sclerosis, Lambert-Eaton Myasthenic Syndrome, motor neuron disease, muscular atrophy such as spinal muscular atrophy, Charcot-Marie Disease and Werdnig-Hoffmann Disease, Postpoliomyelitis Syndrome, Muscular Dystrophy, Myasthenia Gravis, Myotonia Atrophica, Myotonia Confenita, Nemaline Myopathy, Familial Periodic Paralysis, Multiplex

Paramyloclonus, Tropical Spastic Paraparesis and Stiff-Man Syndrome, peripheral nervous system diseases such as acrodynia, amyloid neuropathies, autonomic nervous system diseases such as Adie's Syndrome, Barre-Lieou Syndrome, Familial Dysautonomia, Horner's Syndrome, Reflex Sympathetic Dystrophy and Shy-Drager Syndrome, Cranial Nerve Diseases such as Acoustic Nerve Diseases such as Acoustic Neuroma which includes Neurofibromatosis 2, Facial Nerve Diseases such as Facial Neuralgia, Melkersson-Rosenthal Syndrome, ocular motility disorders which includes amblyopia, nystagmus, oculomotor nerve paralysis, ophthalmoplegia such as Duane's Syndrome, Horner's Syndrome, Chronic Progressive External Ophthalmoplegia which includes Kearns Syndrome, Strabismus such as Esotropia and Exotropia, Oculomotor Nerve Paralysis, Optic Nerve Diseases such as Optic Atrophy which includes Hereditary Optic Atrophy, Optic Disk Drusen, Optic Neuritis such as Neuromyelitis Optica, Papilledema, Trigeminal Neuralgia, Vocal Cord Paralysis, Demyelinating Diseases such as Neuromyelitis Optica and Swayback, Diabetic neuropathies such as diabetic foot, nerve compression syndromes such as carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome such as cervical rib syndrome, ulnar nerve compression syndrome, neuralgia such as causalgia, cervico-brachial neuralgia, facial neuralgia and trigeminal neuralgia, neuritis such as experimental allergic neuritis, optic neuritis, polyneuritis, polyradiculoneuritis and radiculities such as polyradiculitis, hereditary motor and sensory neuropathies such as Charcot-Marie Disease, Hereditary Optic Atrophy, Refsum's Disease, Hereditary Spastic Paraplegia and Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies which include Congenital Analgesia and Familial Dysautonomia, POEMS Syndrome, Sciatica, Gustatory Sweating and Tetany).

Infectious Disease

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Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

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Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papiloma virus, Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiollitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia, polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat: meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat patients nonresponsive to one or more other commercially available hepatitis vaccines. In a further specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat AIDS.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, include, but not limited to, the following Gram-Negative and Gram-positive bacteria and bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Cryptococcus neoformans, Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia

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(e.g., Borrelia burgdorferi, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, E. coli (e.g., Enterotoxigenic E. coli and Enterohemorrhagic E. coli), Enterobacteriaceae (Klebsiella, Salmonella (e.g., Salmonella typhi, and Salmonella paratyphi), Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Mycobacterium leprae, Vibrio cholerae, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Menigococcal), Meisseria meningitidis, Pasteurellacea Infections (e.g., Actinobacillus, Heamophilus (e.g., Heamophilus influenza type B), Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, Shigella spp., Staphylococcal, Meningiococcal, Pneumococcal and Streptococcal (e.g., Streptococcus pneumoniae and Group B Streptococcus). These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis (e.g., mengitis types A and B), Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. Polynucleotides or polypeptides, agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, Ppolynucleotides, polypeptides, agonists or antagonists of the invention are used to treat: tetanus, Diptheria, botulism, and/or meningitis type B.

Moreover, parasitic agents causing disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas and Sporozoans (e.g., Plasmodium virax, Plasmodium falciparium, Plasmodium malariae and Plasmodium ovale). These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic

infections (e.g., AIDS related), malaria, pregnancy complications, and toxoplasmosis. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

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Regeneration

WO 00/55173

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteocarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

284

Similarly, nerve and brain tissue could also be regenerated by using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stoke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotides or polypeptides, as well as agonists or antagonists of the present invention.

Chemotaxis

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Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may have chemotaxis activity. A chemotaxic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may increase chemotaxic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotaxic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could be used as an inhibitor of chemotaxis.

Binding Activity

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

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Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide. Preferred cells include cells from mammals, yeast, Drosophila, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

Additionally, the receptor to which the polypeptide of the present invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand

panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the polypeptides, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are exposed to the polypeptide of the present invention, after they have been labelled. The polypeptides can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

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Following fixation and incubation, the slides are subjected to auto-radiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

As an alternative approach for receptor identification, the labeled polypeptides can be photoaffinity linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE analysis and exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the polypeptide of the present invention thereby effectively generating agonists and antagonists of the polypeptide of the present invention. See generally, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., et al., Curr. Opinion Biotechnol. 8:724-33 (1997); Harayama, S. Trends Biotechnol. 16(2):76-82 (1998); Hansson, L. O., et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R. Biotechniques 24(2):308-13 (1998) (each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and corresponding polypeptides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides and corresponding

polypeptides may be alterred by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptide of the present invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

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Other preferred fragments are biologically active fragments of the polypeptide of the present invention. Biologically active fragments are those exhibiting activity similár, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Additionally, this invention provides a method of screening compounds to identify those which modulate the action of the polypeptide of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, a the polypeptide of the present invention, the compound to be screened and ³[H] thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the uptake of ³[H] thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of ³[H] thymidine. Both agonist and antagonist compounds may be identified by this procedure.

In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the

present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from suitably manipulated cells or tissues.

Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the present invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the present invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

Targeted Delivery

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In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a polypeptide of the invention, or cells expressing a cell bound form of a polypeptide of the invention.

As discussed herein, polypeptides or antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method

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for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, Pseudomonas exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

25 **Drug Screening**

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Further contemplated is the use of the polypeptides of the present invention, or the polynucleotides encoding these polypeptides, to screen for molecules which modify the activities of the polypeptides of the present invention. Such a method would include contacting the polypeptide of the present invention with a selected compound(s) suspected of having antagonist or agonist activity, and assaying the activity of these polypeptides following binding.

This invention is particularly useful for screening therapeutic compounds by using the

polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and a polypeptide of the present invention.

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Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the polypeptides of the present invention. These methods comprise contacting such an agent with a polypeptide of the present invention or a fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the polypeptides of the present invention.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the present invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with polypeptides of the present invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the present invention specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

Antisense And Ribozvme (Antagonists)

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In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to nucleotide sequences contained in the cDNA contained in the related cDNA clone identified in Table 1. In one embodiment, antisense sequence is generated internally, by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, J., Neurochem. 56:560 (1991). Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, J., Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., Nucleic Acids Research 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These experiments were performed in vitro by incubating cells with the oligoribonucleotide. A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked by an EcoR1 site on the 5 end and a HindIII site on the 3 end. Next, the pair of oligonucleotides is heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCl pH 7.5, 10mM MgCl2, 10MM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoR1/Hind III site of the retroviral vector PMV7 (WO 91/15580).

For example, the 5' coding portion of a polynucleotide that encodes the polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the

292

production of the receptor. The antisense RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

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In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the antisense nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding the polypeptide of the present invnetion or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, Nature 29:304-310 (1981), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., Cell 22:787-797 (1980), the herpes thymidine promoter (Wagner et al., Proc. Natl. Acad. Sci. U.S.A. 78:1441-1445 (1981), the regulatory sequences of the metallothionein gene (Brinster, et al., Nature 296:39-42 (1982)), etc.

The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of the present invention. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

Oligonucleotides that are complementary to the 5' end of the message, e.g., the 5' untranslated sequence up to and including the AUG initiation codon, should work most

efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., 1994, Nature 372:333-335. Thus, oligonucleotides complementary to either the 5'- or 3'- non- translated, non-coding regions of polynucleotide sequences described herein could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of mRNA of the present invention, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

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The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors in vivo), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:6553-6556; Lemaitre et al., 1987, Proc. Natl. Acad. Sci. 84:648-652; PCT Publication No. WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication No. WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, e.g., Krol et al., 1988, BioTechniques 6:958-976) or intercalating agents. (See, e.g., Zon, 1988, Pharm. Res. 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine,

2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

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In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other (Gautier et al., 1987, Nucl. Acids Res. 15:6625-6641). The oligonucleotide is a 2'-0-methylribonucleotide (Inoue et al., 1987, Nucl. Acids Res. 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue et al., 1987, FEBS Lett. 215:327-330).

Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. (1988, Nucl. Acids Res. 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. U.S.A. 85:7448-7451), etc.

While antisense nucleotides complementary to the coding region sequence could be used, those complementary to the transcribed untranslated region are most preferred.

Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science 247:1222-1225 (1990). While ribozymes that cleave mRNA at

site specific recognition sequences can be used to destroy mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, Nature 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within the nucleotide sequence of SEQ ID NO:X. Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

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As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express in vivo. DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation or growth.

The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and prevent the proliferation of epithelial lens cells after extracapsular cataract surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirous in cases such as restenosis after balloon angioplasty.

The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

The antagonist/agonist may also be employed to treat the diseases described herein.

Thus, the invention provides a method of treating disorders or diseases, including but not limited to the disorders or diseases listed throughout this application, associated with overexpression of a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

5 Other Activities

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A polypeptide, polynucleotide, agonist, or antagonist of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. The polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed stimulate neuronal growth and to treat and prevent neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's disease, Parkinson's disease, and AIDS-related complex. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may have the ability to stimulate chondrocyte growth, therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

297

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, caricadic rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

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Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions identified as "Start" and "End" in columns 7 and 8 as defined for SEQ ID NO:X in Table 1.

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Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X in the range of positions identified as "Start" and "End" in columns 7 and 8 as defined for SEQ ID NO:X in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which comprises a cDNA clone contained in the deposit.

299

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of the cDNA in the related cDNA clone contained in the deposit.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of an open reading frame sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

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Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a

300

nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

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Also preferred is the above method for identifying the species, tissue or cell type of a biological sample which comprises a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleotide sequence of SEQ ID NO:X; or the cDNA in the related cDNA clone identified in Table 1 which encodes a protein, wherein the method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence of the cDNA in the related cDNA clone contained in the deposit.

Also preferred is the above method for diagnosing a pathological condition which comprises a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the

group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

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Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a DNA microarray or "chip" of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 100, 150, 200, 250, 300, 500, 1000, 2000, 3000 or 4000 nucleotide sequences, wherein at least one sequence in said DNA microarray or "chip" is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the cDNA clone referenced in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

302

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a portion of said polypeptide encoded by the cDNA clone referenced in Table 1; a polypeptide encoded by SEQ ID NO:X; and/or the polypeptide sequence of SEQ ID NO:Y.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

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Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in

303

a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

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Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleic acid sequence identified in Table 1 encoding a polypeptide, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of:

polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

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Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a human protein comprising an amino acid sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an increased level of a protein activity, which method comprises administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to increase the level of said protein activity in said individual.

Also preferred is a method of treatment of an individual in need of a decreased level of a protein activity, which method comprised administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to decrease the level of said protein activity in said individual.

305

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

306

Examples

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Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

Each deposited cDNA clone is contained in a plasmid vector. Table 5 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The following correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 5 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

	Vector Used to Construct Library	Corresponding Deposited Plasmid
	Lambda Zap	pBluescript (pBS)
	Uni-Zap XR	pBluescript (pBS)
15	Zap Express	pBK
	lafmid BA	plafmid BA
	pSport1	pSport1
	pCMVSport 2.0	pCMVSport 2.0
	pCMVSport 3.0	pCMVSport 3.0
20	pCR [®] 2.1	pCR [®] 2.1

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3

primer sequences which flank the polylinker region ("S" is for Sacl and "K" is for Kpnl which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the fl origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the fl ori generates sense strand DNA and in the other, antisense.

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Vectors pSport1, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR®2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 5, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited by reference to Table 2 and 5 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone referenced in Table 1.

308

TABLE 5

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HUKA HUKB HUKC HUKD HUKE HUKF HUKG	Human Uterine Cancer	Lambda ZAP II	LP01
HCNA HCNB	Human Colon	Lambda Zap II	LP01
HFFA	Human Fetal Brain, random primed	Lambda Zap II	LP01
HTWA	Resting T-Cell	Lambda ZAP II	LP01
НВQA	Early Stage Human Brain, random primed	Lambda ZAP II	LP01
HLMB HLMF HLMG HLMH HLMI HLMJ HLMM HLMN	breast lymph node CDNA library	Lambda ZAP II	LP01
HCQA HCQB	human colon cancer	Lamda ZAP II	LP01
HMEA HMEC HMED HMEE HMEF HMEG HMEI HMEJ HMEK HMEL	Human Microvascular Endothelial Cells, fract. A	Lambda ZAP II	LP01
HUSA HUSC	Human Umbilical Vein Endothelial Cells, fract. A	Lambda ZAP II	LP01
HLQA HLQB	Hepatocellular Tumor	Lambda ZAP II	LP01
HHGA HHGB HHGC HHGD	Hemangiopericytoma	Lambda ZAP II	LP01
HSDM		Lambda ZAP II	LP01
HUSH	H Umbilical Vein Endothelial Cells, frac A, re-excision	Lambda ZAP II	LP01
HSGS	Salivary gland, subtracted	Lambda ZAP II	LP01
HFXA HFXB HFXC HFXD HFXE HFXF HFXG HFXH	Brain frontal cortex	Lambda ZAP II	LP01
HPQA HPQB HPQC	PERM TF274	Lambda ZAP II	LP01
HFXJ HFXK	Brain Frontal Cortex, re-excision	Lambda ZAP II	LP01
HCWA HCWB HCWC HCWD HCWE HCWF HCWG HCWH HCWI HCWJ HCWK	CD34 positive cells (Cord Blood)	ZAP Express	LP02
HCUA HCUB HCUC	CD34 depleted Buffy Coat (Cord Blood)	ZAP Express	LP02
HRSM	A-14 cell line	ZAP Express	LP02
HRSA	A1-CELL LINE	ZAP Express	LP02
HCUD HCUE HCUF HCUG HCUH HCUI	CD34 depleted Buffy Coat (Cord Blood), re-excision	ZAP Express	LP02
HBXE HBXF HBXG	H. Whole Brain #2, re-excision	ZAP Express	LP02
HRLM	L8 cell line	ZAP Express	LP02
НВХА НВХВ НВХС НВХД	Human Whole Brain #2 - Oligo dT > 1.5Kb	ZAP Express	LP02
HUDA HUDB HUDC	Testes	ZAP Express	LP02
ннтм ннто	H. hypothalamus, frac A;re-excision	ZAP Express	LP02
HHTL	H. hypothalamus, frac A	ZAP Express	LP02
HASA HASD	Human Adult Spleen	Uni-ZAP XR	LP03
HFKC HFKD HFKE HFKF HFKG	Human Fetal Kidney	Uni-ZAP XR	LP03
HE8A HE8B HE8C HE8D HE8E HE8F HE8M HE8N	Human 8 Week Whole Embryo	Uni-ZAP XR	LP03
HGBA HGBD HGBE HGBF HGBG HGBH HGBI		Uni-ZAP XR	LP03
HLHA HLHB HLHC HLHD HLHE HLHF HLHG HLHH HLHQ		Uni-ZAP XR	LP03
HPMA HPMB HPMC HPMD HPME HPMF HPMG HPMH	Human Placenta	Uni-ZAP XR	LP03

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HPRA HPRB HPRC HPRD	Human Prostate	Uni-ZAP XR	LP03
HSIA HSIC HSID HSIE	Human Adult Small Intestine	Uni-ZAP XR	LP03
HTEA HTEB HTEC HTED HTEE HTEF HTEG HTEH HTEI HTEJ HTEK	Human Testes	Uni-ZAP XR	LP03
HTPA HTPB HTPC HTPD HTPE	Human Pancreas Tumor	Uni-ZAP XR	LP03
HTTA HTTB HTTC HTTD HTTE HTTF	Human Testes Tumor	Uni-ZAP XR	LP03
НАРА НАРВ НАРС НАРМ	Human Adult Pulmonary	Uni-ZAP XR	LP03
HETA HETB HETC HETD HETE HETF HETG HETH HETI	Human Endometrial Tumor	Uni-ZAP XR	LP03
HHFB HHFC HHFD HHFE HHFF HHFG HHFH HHFI	Human Fetal Heart	Uni-ZAP XR	LP03
ННРВ ННРС ННРО ННРЕ ННРГ ННРG ННРН	Human Hippocampus	Uni-ZAP XR	LP03
HCE1 HCE2 HCE3 HCE4 HCE5 HCEB HCEC HCED HCEE HCEF HCEG	Human Cerebellum	Uni-ZAP XR	LP03
HUVB HUVC HUVD HUVE	Human Umbilical Vein, Endo. remake	Uni-ZAP XR	LP03
HSTA HSTB HSTC HSTD	Human Skin Tumor	Uni-ZAP XR	LP03
HTAA HTAB HTAC HTAD HTAE	Human Activated T-Cells	Uni-ZAP XR	LP03
HFEA HFEB HFEC	Human Fetal Epithelium (Skin)	Uni-ZAP XR	LP03
НЈРА НЈРВ НЈРС НЈРО	HUMAN JURKAT MEMBRANE BOUND POLYSOMES	Uni-ZAP XR	LP03
HESA	Human epithelioid sarcoma	Uni-Zap XR	LP03
HLTA HLTB HLTC HLTD HLTE HLTF	Human T-Cell Lymphoma	Uni-ZAP XR	LP03
HFTA HFTB HFTC HFTD	Human Fetal Dura Mater	Uni-ZAP XR	LP03
HRDA HRDB HRDC HRDD HRDE HRDF	Human Rhabdomyosarcoma	Uni-ZAP XR	LP03
НСЛА НСАВ НСЛС	Cem cells cyclohexamide treated	Uni-ZAP XR	LP03
HRGA HRGB HRGC HRGD	Raji Cells, cyclohexamide treated	Uni-ZAP XR	LP03
HSUA HSUB HSUC HSUM	Supt Cells, cyclohexamide treated	Uni-ZAP XR	LP03
HT4A HT4C HT4D	Activated T-Cells, 12 hrs.	Uni-ZAP XR	LP03
HE9A HE9B HE9C HE9D HE9E HE9F HE9G HE9H HE9M HE9N	Nine Week Old Early Stage Human	Uni-ZAP XR	LP03
HATA HATB HATC HATD HATE	Human Adrenal Gland Tumor	Uni-ZAP XR	LP03
HT5A	Activated T-Cells, 24 hrs.	Uni-ZAP XR	LP03
IFGA HFGM	Human Fetal Brain	Uni-ZAP XR	LP03
HNEA HNEB HNEC HNED HNEE	Human Neutrophil	Uni-ZAP XR	LP03
HBGB HBGD	Human Primary Breast Cancer	Uni-ZAP XR	LP03
IBNA HBNB	Human Normal Breast	Uni-ZAP XR	LP03
HCAS	Cem Cells, cyclohexamide treated, subtra	Uni-ZAP XR	LP03
HPS	Human Hippocampus, subtracted	pBS	LP03
IKCS HKCU	Human Colon Cancer, subtracted	pBS	LP03
IRGS	Raji cells, cyclohexamide treated, subtracted	pBS	LP03
ISUT	Supt cells, cyclohexamide treated, differentially expressed	pBS	LP03
IT4S	Activated T-Cells, 12 hrs, subtracted	Uni-ZAP XR	LP03
ICDA HCDB HCDC HCDD HCDE	Human Chondrosarcoma	Uni-ZAP XR	LP03
HOAA HOAB HOAC	Human Osteosarcoma	Uni-ZAP XR	LP03
ITLA HTLB HTLC HTLD HTLE	Human adult testis, large inserts	Uni-ZAP XR	LP03

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HTLF			
HLMA HLMC HLMD	Breast Lymph node cDNA library	Uni-ZAP XR	LP03
H6EA H6EB H6EC	HL-60, PMA 4H	Uni-ZAP XR	LP03
HTXA HTXB HTXC HTXD HTXE HTXF HTXG HTXH	Activated T-Cell (12hs)/Thiouridine	Uni-ZAP XR	LP03
HNFA HNFB HNFC HNFD HNFE HNFF HNFG HNFH HNFJ	Human Neutrophil, Activated	Uni-ZAP XR	LP03
нтов нтос	HUMAN TONSILS, FRACTION 2	Uni-ZAP XR	LP03
НМСВ	Human OB MG63 control fraction I	Uni-ZAP XR	LP03
НОРВ	Human OB HOS control fraction I	Uni-ZAP XR	LP03
HORB	Human OB HOS treated (10 nM E2) fraction I	Uni-ZAP XR	LP03
HSVA HSVB HSVC	Human Chronic Synovitis	Uni-ZAP XR	LP03
HROA	HUMAN STOMACH	Uni-ZAP XR	LP03
НВЈА НВЈВ НВЈС НВЈО НВЈЕ НВЈҒ НВЈС НВЈН НВЈІ НВЈЈ НВЈК	HUMAN B CELL LYMPHOMA	Uni-ZAP XR	LP03
HCRA HCRB HCRC	human corpus colosum	Uni-ZAP XR	LP03
HODA HODB HODC HODD	human ovarian cancer	Uni-ZAP XR	LP03
HDSA	Dermatofibrosarcoma Protuberance	Uni-ZAP XR	LP03
HMWA HMWB HMWC HMWD HMWE HMWF HMWG HMWH HMWI HMWJ	Bone Marrow Cell Line (RS4;11)	Uni-ZAP XR	LP03
HSOA	stomach cancer (human)	Uni-ZAP XR	LP03
HERA	SKIN	Uni-ZAP XR	LP03
HMDA	Brain-medulloblastoma	Uni-ZAP XR	LP03
HGLA HGLB HGLD	Glioblastoma	Uni-ZAP XR	LP03
HEAA	H. Atrophic Endometrium	Uni-ZAP XR	LP03
НВСА НВСВ	H. Lymph node breast Cancer	Uni-ZAP XR	LP03
HPWT	Human Prostate BPH, re-excision	Uni-ZAP XR	LP03
HFVG HFVH HFVI	Fetal Liver, subtraction II	pBS	LP03
HNFI	Human Neutrophils, Activated, re- excision	pBS	LP03
НВМВ НВМС НВМD	Human Bone Marrow, re-excision	pBS	LP03
НКМІ НКММ НКММ	H. Kidney Medulla, re-excision	pBS	LP03
HKIX HKIY	H. Kidney Cortex, subtracted	pBS	LP03
HADT	H. Amygdala Depression, subtracted	pBS	LP03
H6AS	HI-60, untreated, subtracted	Uni-ZAP XR	LP03
H6ES	HL-60, PMA 4H, subtracted	Uni-ZAP XR	LP03
H6BS	HL-60, RA 4h, Subtracted	Uni-ZAP XR	LP03
H6CS	HL-60, PMA 1d, subtracted	Uni-ZAP XR	LP03
НТХЈ НТХК	Activated T-cell(12h)/Thiouridine-re- excision	Uni-ZAP XR	LP03
HMSA HMSB HMSC HMSD HMSE HMSF HMSG HMSH HMSI HMSJ HMSK	Monocyte activated	Uni-ZAP XR	LP03
HAGA HAGB HAGC HAGD HAGE HAGF	Human Amygdala	Uni-ZAP XR	LP03
HSRA HSRB HSRE	STROMAL -OSTEOCLASTOMA	Uni-ZAP XR	LP03
HSRD HSRF HSRG HSRH	Human Osteoclastoma Stromal Cells - unamplified	Uni-ZAP XR	LP03
HSQA HSQB HSQC HSQD HSQE	Stromal cell TF274	Uni-ZAP XR	LP03

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HSQF HSQG			
HSKA HSKB HSKC HSKD HSKE HSKF HSKZ	Smooth muscle, serum treated	Uni-ZAP XR	LP03
HSLA HSLB HSLC HSLD HSLE HSLF HSLG	Smooth muscle control	Uni-ZAP XR	LP03
HSDA HSDD HSDE HSDF HSDG HSDH	Spinal cord	Uni-ZAP XR	LP03
HPWS	Prostate-BPH subtracted II	pBS	LP03
HSKW HSKX HSKY	Smooth Muscle- HASTE normalized	pBS	LP03
HFPB HFPC HFPD	H. Frontal cortex,epileptic;re-excision	Uni-ZAP XR	LP03
HSDI HSDJ HSDK	Spinal Cord, re-excision	Uni-ZAP XR	LP03
HSKN HSKO	Smooth Muscle Serum Treated, Norm	pBS	LP03
HSKG HSKH HSKI	Smooth muscle, serum induced,re-exc	pBS	LP03
HFCA HFCB HFCC HFCD HFCE HFCF	Human Fetal Brain	Uni-ZAP XR	LP04
HPTA HPTB HPTD	Human Pituitary	Uni-ZAP XR	LP04
HTHB HTHC HTHD	Human Thymus	Uni-ZAP XR	LP04
HE6B HE6C HE6D HE6E HE6F HE6G HE6S	Human Whole Six Week Old Embryo	Uni-ZAP XR	LP04
HSSA HSSB HSSC HSSD HSSE HSSF HSSG HSSH HSSI HSSJ HSSK		Uni-ZAP XR	LP04
HE7T	7 Week Old Early Stage Human, subtracted	Uni-ZAP XR	LP04
НЕРА НЕРВ НЕРС	Human Epididymus	Uni-ZAP XR	LP04
HSNA HSNB HSNC HSNM HSNN	Human Synovium	Uni-ZAP XR	LP04
HPFB HPFC HPFD HPFE	Human Prostate Cancer, Stage C fraction	Uni-ZAP XR	LP04
HE2A HE2D HE2E HE2H HE2I HE2M HE2N HE2O	12 Week Old Early Stage Human	Uni-ZAP XR	LP04
HE2B HE2C HE2F HE2G HE2P HE2Q	12 Week Old Early Stage Human, II	Uni-ZAP XR	LP04
HPTS HPTT HPTU	Human Pituitary, subtracted	Uni-ZAP XR	LP04
HAUA HAUB HAUC	Amniotic Cells - TNF induced	Uni-ZAP XR	LP04
HAQA HAQB HAQC HAQD	Amniotic Cells - Primary Culture	Uni-ZAP XR	LP04
HWTA HWTB HWTC	wilm's tumor	Uni-ZAP XR	LP04
HBSD	Bone Cancer, re-excision	Uni-ZAP XR	LP04
HSGB	Salivary gland, re-excision	Uni-ZAP XR	LP04
HSJA HSJB HSJC	Smooth muscle-ILb induced	Uni-ZAP XR	LP04
HSXA HSXB HSXC HSXD	Human Substantia Nigra	Uni-ZAP XR	LP04
HSHA HSHB HSHC	Smooth muscle, IL1b induced	Uni-ZAP XR	LP04
HOUA HOUB HOUC HOUD HOUE	Adipocytes	Uni-ZAP XR	LP04
HPWA HPWB HPWC HPWD HPWE	Prostate BPH	Uni-ZAP XR	LP04
HELA HELB HELC HELD HELE HELF HELG HELH	Endothelial cells-control	Uni-ZAP XR	LP04
	Endothelial-induced	Uni-ZAP XR	LP04
	Human Brain, Striatum	Uni-ZAP XR	LP04
HHSA HHSB HHSC HHSD HHSE	Human Hypothalmus, Schizophrenia	Uni-ZAP XR	LP04
		Uni-ZAP XR	LP04
	Neutrophils IL-1 and LPS induced	Uni-ZAP XR	LP04
	STRIATUM DEPRESSION	Uni-ZAP XR	LP04

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
ннрт	Hypothalamus	Uni-ZAP XR	LP04
HSAT HSAU HSAV HSAW HSAX HSAY HSAZ	Anergic T-cell	Uni-ZAP XR	LP04
HBMS HBMT HBMU HBMV HBMW HBMX	Bone marrow	Uni-ZAP XR	LP04
HOEA HOEB HOEC HOED HOEE HOEF HOEJ	Osteoblasts	Uni-ZAP XR	LP04
HAIA HAIB HAIC HAID HAIE HAIF	Epithelial-TNFa and INF induced	Uni-ZAP XR	LP04
HTGA HTGB HTGC HTGD	Apoptotic T-cell	Uni-ZAP XR	LP04
HMCA HMCB HMCC HMCD HMCE	Macrophage-oxLDL	Uni-ZAP XR	LP04
HMAA HMAB HMAC HMAD HMAE HMAF HMAG	Macrophage (GM-CSF treated)	Uni-ZAP XR	LP04
НРНА	Normal Prostate	Uni-ZAP XR	LP04
НРІА НРІВ НРІС	LNCAP prostate cell line	Uni-ZAP XR	LP04
НРЈА НРЈВ НРЈС	PC3 Prostate cell line	Uni-ZAP XR	LP04
HOSE HOSF HOSG	Human Osteoclastoma, re-excision	Uni-ZAP XR	LP04
HTGE HTGF	Apoptotic T-cell, re-excision	Uni-ZAP XR	LP04
НМАЈ НМАК	H Macrophage (GM-CSF treated), re- excision	Uni-ZAP XR	LP04
HACB HACC HACD	Human Adipose Tissue, re-excision	Uni-ZAP XR	LP04
HFPA	H. Frontal Cortex, Epileptic	Uni-ZAP XR	LP04
HFAA HFAB HFAC HFAD HFAE	Alzheimers, spongy change	Uni-ZAP XR	LP04
HFAM	Frontal Lobe, Dementia	Uni-ZAP XR	LP04
НМІА НМІВ НМІС	Human Manic Depression Tissue	Uni-ZAP XR	LP04
HTSA HTSE HTSF HTSG HTSH	Human Thymus	pBS	LP05
НРВА НРВВ НРВС НРВО НРВЕ	Human Pineal Gland	pBS	LP05
HSAA HSAB HSAC	HSA 172 Cells	pBS	LP05
HSBA HSBB HSBC HSBM	HSC172 cells	pBS	LP05
HJAA HJAB HJAC HJAD	Jurkat T-cell G1 phase	pBS	LP05
НЈВА НЈВВ НЈВС НЈВD	Jurkat T-Cell, S phase	pBS	LP05
HAFA HAFB	Aorta endothelial cells + TNF-a	pBS	LP05
HAWA HAWB HAWC	Human White Adipose	pBS	LP05
HTNA HTNB	Human Thyroid	pBS	LP05
AONA	Normal Ovary, Premenopausal	pBS	LP05
ARA HARB	Human Adult Retina	pBS	LP05
ILJA HLJB	Human Lung	pCMVSport 1	LP06
ЮГМ НОГО	H. Ovarian Tumor, II, OV5232	pCMVSport 2.0	LP07
HOGA HOGB HOGC	OV 10-3-95	pCMVSport 2.0	LP07
ICGL	CD34+cells, II	pCMVSport 2.0	LP07
IDLA	Hodgkin's Lymphoma I	pCMVSport 2.0	LP07
IDTA HDTB HDTC HDTD HDTE	Hodgkin's Lymphoma II	pCMVSport 2.0	LP07
HKAA HKAB HKAC HKAD HKAE HKAF HKAG HKAH	Keratinocyte	pCMVSport2.0	LP07
СІМ	CAPFINDER, Crohn's Disease, lib 2	pCMVSport 2.0	LP07
IKAL	Keratinocyte, lib 2	pCMVSport2.0	LP07
łkat	Keratinocyte, lib 3	pCMVSport2.0	LP07
INDA	Nasal polyps	pCMVSport2.0	LP07
IDRA	H. Primary Dendritic Cells,lib 3	pCMVSport2.0	LP07

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
НОНА НОНВ НОНС	Human Osteoblasts II	pCMVSport2.0	LP07
HLDA HLDB HLDC	Liver, Hepatoma	pCMVSport3.0	LP08
HLDN HLDO HLDP	Human Liver, normal	pCMVSport3.0	LP08
НМТА	pBMC stimulated w/ poly I/C	pCMVSport3.0	LP08
HNTA	NTERA2. control	pCMVSport3.0	LP08
HDPA HDPB HDPC HDPD HDPF HDPG HDPH HDPI HDPJ HDPK	Primary Dendritic Cells, lib 1	pCMVSport3.0	LP08
HDPM HDPN HDPO HDPP	Primary Dendritic cells,frac 2	pCMVSport3.0	LP08
HMUA HMUB HMUC	Myoloid Progenitor Cell Line	pCMVSport3.0	LP08
HHEA HHEB HHEC HHED	T Cell helper I	pCMVSport3.0	LP08
НЕМ ННЕО ННЕР	T cell helper II	pCMVSport3.0	LP08
HEQA HEQB HEQC	Human endometrial stromal cells	pCMVSport3.0	LP08
НЈМА НЈМВ	Human endometrial stromal cells-treated with progesterone	pCMVSport3.0	LP08
HSWA HSWB HSWC	Human endometrial stromal cells-treated with estradiol		LP08
HSYA HSYB HSYC		pCMVSport3.0	LP08
HLWA HLWB HLWC	.1	pCMVSport3.0	LP08
HRAA HRAB HRAC	L	pCMVSport3.0	LP08
нмтм	PCR, pBMC I/C treated	PCRII	LP09
НМЈА	H. Meniingima, M6	pSport I	LP10
НМКА НМКВ НМКС НМКД НМКЕ	H. Meningima, MI	pSport I	LP10
HUSG HUSI	Human umbilical vein endothelial cells, IL-4 induced	pSport 1	LP10
HUSX HUSY	Human Umbilical Vein Endothelial Cells, uninduced	pSport I	LP10
HOFA	Ovarian Tumor I, OV5232	pSport I	LP10
HCFA HCFB HCFC HCFD	T-Cell PHA 16 hrs	pSport I	LP10
HCFL HCFM HCFN HCFO	T-Cell PHA 24 hrs	pSport I	LP10
IADA HADC HADD HADE HADF IADG	Human Adipose	pSport I	LP10
HOVA HOVB HOVC	Human Ovary	pSport 1	LP10
HTWB HTWC HTWD HTWE HTWF		pSport I	LP10
ІММА		pSport I	LP10
ILYA HLYB HLYC HLYD HLYE	1 5	pSport 1	LP10
łCGA	CD34+ cell, I	pSport 1	LP10
IEOM HEON	Human Eosinophils	pSport 1	LP10
HTDA	Human Tonsil, Lib 3	pSport I	LP10
ISPA	Salivary Gland, Lib 2	pSport I	LP10
СНА НСНВ НСНС	Breast Cancer cell line, MDA 36	pSport 1	LP10
ІСНМ НСНИ	Breast Cancer Cell line, angiogenic	pSport I	LP10
icia	Crohn's Disease	pSport I	LP10
IDAA HDAB HDAC	HEL cell line	pSport I	LP10
IABA	Human Astrocyte	pSport I	LP10
UFA HUFB HUFC	<u> </u>	pSport I	LP10
INTM		pSport I	LP10
IDQA	Primary Dendritic cells, CapFinder2, frac		LP10
IDQM	Primary Dendritic Cells, CapFinder, frac	pSport 1	LP10
	<u> </u>		

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
	2		
HLDX	Human Liver, normal.CapFinder	pSport 1	LP10
HULA HULB HULC	Human Dermal Endothelial Cells untreated	pSport1	LP10
HUMA	Human Dermai Endothelial cells.treated	pSport1	LP10
НСЈА	Human Stromal Endometrial fibroblasts, untreated	pSport1	LP10
НСЈМ		pSport1	LP10
HEDA	Human Stromal endometrial fibroblasts, treated with progesterone	pSport1	LP10
HFNA	Human ovary tumor cell OV350721	pSport1	LP10
HKGA HKGB HKGC HKGD	Merkel Cells	pSportl	LP10
HISA HISB HISC	Pancreas Islet Cell Tumor	pSport1	LP10
HLSA	Skin, burned	pSport1	LP10
HBZA	Prostate.BPH, Lib 2	pSport I	LP10
1BZS	Prostate BPH,Lib 2, subtracted	pSport 1	LP10
IFIA HFIB HFIC	Synovial Fibroblasts (control)	pSport 1	LP10
IFIH HFII HFIJ	Synovial hypoxia	pSport I	LP10
HFIT HFIU HFIV	Synovial IL-1/TNF stimulated	pSport I	LP10
IGCA	Messangial cell. frac 1	pSport1	LP10
HMVA HMVB HMVC	Bone Marrow Stromal Cell, untreated	pSport1	LP10
FIX HFIY HFIZ	Synovial Fibroblasts (III/TNF), subt	pSport1	LP10
HFOX HFOY HFOZ	Synovial hypoxia-RSF subtracted	pSport1	LP10
HMQA HMQB HMQC HMQD	Human Activated Monocytes	Uni-ZAP XR	LP11
HLIA HLIB HLIC	Human Liver	pCMVSport I	LP012
HBA HHBB HHBC HHBD HHBE	Human Heart	pCMVSport I	LP012
HBBA HBBB	Human Brain	pCMVSport I	LP012
ALJA HLJB HLJC HLJD HLJE	Human Lung	pCMVSport I	LP012
HOGA HOGB HOGC	Ovarian Tumor	pCMVSport 2.0	LP012
MUTH	Human Tonsils, Lib 2	pCMVSport 2.0	LP012
HAMF HAMG	KMH2	pCMVSport 3.0	LP012
АЈА НАЈВ НАЈС	L428	pCMVSport 3.0	LP012
IWBA HWBB HWBC HWBD HWBE	Dendritic cells, pooled	pCMVSport 3.0	LP012
WAA HWAB HWAC HWAD HWAE	Human Bone Marrow, treated	pCMVSport 3.0	LP012
IYAA HYAB HYAC	B Cell lymphoma	pCMVSport 3.0	LP012
чинд нинн нинг	Healing groin wound, 6.5 hours post incision	pCMVSport 3.0	LP012
нинр нино нинг	Healing groin wound; 7.5 hours post incision	pCMVSport 3.0	LP012
iarm	Healing groin wound - zero hr post- incision (control)	pCMVSport 3.0	LP012
НВІМ	Olfactory epithelium; nasalcavity	pCMVSport 3.0	LP012
łWDA	Healing Abdomen wound; 70&90 min post incision	pCMVSport 3.0	LP012
łwea	incision	pCMVSport 3.0	LP012
IWJA	Healing Abdomen Wound:21&29 days	pCMVSport 3.0	LP012
INAL	Human Tongue, frac 2	pSporti	LP012
łMJA	H. Meniingima, M6	pSport1	LP012
HMKA HMKB HMKC HMKD HMKE	H. Meningima, MI	pSporti	LP012

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Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HOFA	Ovarian Tumor I. OV5232	pSport!	LP012
HCFA HCFB HCFC HCFD	T-Cell PHA 16 hrs	pSport1	LP012
HCFL HCFM HCFN HCFO	T-Cell PHA 24 hrs	pSport1	LP012
НММА НММВ НММС	Spleen metastic melanoma	pSport1	LP012
HTDA	Human Tonsil, Lib 3	pSport1	LP012
HDBA	Human Felal Thymus	pSport1	LP012
HDUA	Pericardium	pSport1	LP012
HBZA	Prostate BPH, Lib 2	pSporti	LP012
HWCA	Larynx tumor	pSport I	LP012
HWKA	Normal lung	pSport1	LP012
HSMB	Bone marrow stroma,treated	pSport1	LP012
НВНМ	Normal trachea	pSportI	LP012
HLFC	Human Larynx	pSport1	LP012
HLRB	Siebben Polyposis	pSport1	LP012
HNIA	Mammary Gland	pSport1	LP012
HNJB	Palate carcinoma	pSport1	LP012
HNKA	Palate normal	pSporti	LP012
HMZA			
HABG	Pharynx carcinoma Cheek Carcinoma	pSport1	LP012
HMZM		pSport1	LP012
HDRM	Pharynx Carcinoma	pSport1	LP012
HVAA	Larynx Carcinoma Pancreas normal PCA4 No	pSport1	LP012
		pSport1	LP012
HICA	Fongue carcinoma	pSport1	LP012
HUKA HUKB HUKC HUKD HUKE	Human Uterine Cancer	Lambda ZAP II	LP013
HFFA	Human Fetal Brain, random primed	Lambda ZAP II	LP013
HTUA	Activated T-cell labeled with 4-thioluri	Lambda ZAP II	LP013
HBQA	Early Stage Human Brain, random primed	Lambda ZAP II	LP013
НМЕВ	Human microvascular Endothelial cells, fract. B	Lambda ZAP II	LP013
HUSH	Human Umbilical Vein Endothelial cells, fract. A, re-excision	Lambda ZAP II	LP013
HLQC HLQD	Hepatocellular tumor, re-excision	Lambda ZAP II	LP013
HTWJ HTWK HTWL	Resting T-cell, re-excision	Lambda ZAP II	LP013
HF6S	Human Whole 6 week Old Embryo (II), subt	pBluescript	LP013
HHPS	Human Hippocampus, subtracted	pBluescript	LP013
HLIS	LNCAP, differential expression	pBluescript	LP013
HLHS HLHT	Early Stage Human Lung, Subtracted	pBluescript	LP013
HSUS	Supt cells, cyclohexamide treated, subtracted	pBluescript	LP013
HSUT	Supt cells, cyclohexamide treated, differentially expressed	pBluescript	LP013
HSDS	H. Striatum Depression, subtracted	pBluescript	LP013
HPTZ	Human Pituitary, Subtracted VII	pBluescript	LP013
HSDX	H. Striatum Depression, subt II	pBluescript	LP013
HSDZ	H. Striatum Depression, subt	pBluescript	LP013
НРВА НРВВ НРВС НРВО НРВЕ	Human Pineal Gland	pBluescript SK-	LP013
HRTA	Colorectal Tumor	pBluescript SK-	LP013
НЅВА НЅВВ НЅВС НЅВМ	HSC172 cells	pBluescript SK-	LP013
HJAA HJAB HJAC HJAD	Jurkat T-cell G1 phase	pBluescript SK-	LP013
НЈВА НЈВВ НЈВС НЈВО	Jurkai T-cell, S1 phase	pBluescript SK-	LP013

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HTNA HTNB	Human Thyroid	pBluescript SK-	LP013
нана нанв	Human Adult Heart	Uni-ZAP XR	LP013
HE6A	Whole 6 week Old Embryo	Uni-ZAP XR	LP013
HFCA HFCB HFCC HFCD HFCE	Human Fetal Brain	Uni-ZAP XR	LP013
HFKC HFKD HFKE HFKF HFKG	Human Fetal Kidney	Uni-ZAP XR	LP013
HGBA HGBD HGBE HGBF HGBG	Human Gall Bladder	Uni-ZAP XR	LP013
HPRA HPRB HPRC HPRD	Human Prostate	Uni-ZAP XR	LP013
HTEA HTEB HTEC HTED HTEE	Human Testes	Uni-ZAP XR	LP013
HTTA HTTB HTTC HTTD HTTE	Human Testes Tumor	Uni-ZAP XR	LP013
НҮВА НҮВВ	Human Fetal Bone	Uni-ZAP XR	LP013
HFLA	Human Fetal Liver	Uni-ZAP XR	LP013
Н Н ГВ ННГС ННГО ННГЕ ННГГ	Human Fetal Heart	Uni-ZAP XR	LP013
HUVB HUVC HUVD HUVE	Human Umbilical Vein, End. remake	Uni-ZAP XR	LP013
Н ТНВ НТ НС НТНО	Human Thymus	Uni-ZAP XR	LP013
HSTA HSTB HSTC HSTD	Human Skin Tumor	Uni-ZAP XR	LP013
HTAA HTAB HTAC HTAD HTAE	Human Activated T-cells	Uni-ZAP XR	LP013
HFEA HFEB HFEC	Human Fetal Epithelium (skin)	Uni-ZAP XR	LP013
НЈРА НЈРВ НЈРС НЈР D	Human Jurkat Membrane Bound Polysomes	Uni-ZAP XR	LP013
HESA	Human Epithelioid Sarcoma	Uni-ZAP XR	LP013
HALS	Human Adult Liver, Subtracted	Uni-ZAP XR	LP013
HFTA HFTB HFTC HFTD	Human Fetal Dura Mater	Uni-ZAP XR	LP013
НСАА НСАВ НСАС	Cem cells, cyclohexamide treated	Uni-ZAP XR	LP013
HRGA HRGB HRGC HRGD	Raji Cells, cyclohexamide treated	Uni-ZAP XR	LP013
НЕ9А НЕ9В НЕ9С НЕ9D НЕ9E	Nine Week Old Early Stage Human	Uni-ZAP XR	LP013
HSFA	Human Fibrosarcoma	Uni-ZAP XR	LP013
HATA HATB HATC HATD HATE	Human Adrenal Gland Tumor	Uni-ZAP XR	LP013
HTRA	Human Trachea Tumor	Uni-ZAP XR	LP013
HE2A HE2D HE2E HE2H HE2I	12 Week Old Early Stage Human	Uni-ZAP XR	LP013
HE2B HE2C HE2F HE2G HE2P	12 Weck Old Early Stage Human, II	Uni-ZAP XR	LP013
HNEA HNEB HNEC HNED HNEE	Human Neutrophil	Uni-ZAP XR	LP013
-IBGA	Human Primary Breast Cancer	Uni-ZAP XR	LP013
HPTS HPTT HPTU	Human Pituitary, subtracted	Uni-ZAP XR	LP013
HMQA HMQB HMQC HMQD	Human Activated Monocytes	Uni-ZAP XR	LP013
НОАА НОАВ НОАС	Human Osteosarcoma	Uni-ZAP XR	LP013
HTOA HTOD HTOE HTOF HTOG	human tonsils	Uni-ZAP XR	LP013
-IMGB	Human OB MG63 control fraction I	Uni-ZAP XR	LP013
ЮРВ	Human OB HOS control fraction I	Uni-ZAP XR	LP013
HOQB	Human OB HOS treated (1 nM E2) fraction I	Uni-ZAP XR	LP013
IAUA HAUB HAUC	Amniotic Cells - TNF induced	Uni-ZAP XR	LP013
IAQA HAQB HAQC HAQD	Amniotic Cells - Primary Culture	Uni-ZAP XR	LP013
IROA HROC	HUMAN STOMACH	Uni-ZAP XR	LP013
нвја нвјв нвјс нвјо нвје	HUMAN B CELL LYMPHOMA	Uni-ZAP XR	LP013
HODA HODB HODC HODD	human ovarian cancer	Uni-ZAP XR	LP013
ICPA	Corpus Callosum	Uni-ZAP XR	LP013
ISOA	stomach cancer (human)	Uni-ZAP XR	LP013
iera	SKIN	Uni-ZAP XR	LP013
IMDA	Brain-medulloblastoma	Uni-ZAP XR	LP013
IGLA HGLB HGLD	Glioblastoma	Uni-ZAP XR	LP013

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HWTA HWTB HWTC	wilm's tumor	Uni-ZAP XR	LP013
HEAA	H. Atrophic Endometrium	Uni-ZAP XR	LP013
HAPN HAPO HAPP HAPQ HAPR	Human Adult Pulmonary:re-excision	Uni-ZAP XR	LP013
HLTG HLTH	Human T-cell lymphoma:re-excision	Uni-ZAP XR	LP013
НАНС НАНО НАНЕ	Human Adult Heart:re-excision	Uni-ZAP XR	LP013
HAGA HAGB HAGC HAGD HAGE	Human Amygdala	Uni-ZAP XR	LP013
HSJA HSJB HSJC	Smooth muscle-ILb induced	Uni-ZAP XR	LP013
ISHA HSHB HSHC	Smooth muscle, IL1b induced	Uni-ZAP XR	LP013
HPWA HPWB HPWC HPWD HPWE	Prostate BPH	Uni-ZAP XR	LP013
НРІА НРІВ НРІС	LNCAP prostate cell line	Uni-ZAP XR	LP013
нрја нрјв нрјс	PC3 Prostate cell line	Uni-ZAP XR	LP013
HBTA	Bone Marrow Stroma, TNF&LPS ind	Uni-ZAP XR	LP013
MCF HMCG HMCH HMCI HMCJ	Macrophage-oxLDL; re-excision	Uni-ZAP XR	LP013
HAGG HAGH HAGI	Human Amygdala;re-excision	Uni-ZAP XR	LP013
IACA	H. Adipose Tissue	Uni-ZAP XR	LP013
-KFB	K562 + PMA (36 hrs).re-excision	ZAP Express	LP013
ICWT HCWU HCWV	CD34 positive cells (cord blood),re-ex	ZAP Express	LP013
HBWA	Whole brain	ZAP Express	LP013
HBXA HBXB HBXC HBXD	Human Whole Brain #2 - Oligo dT >	ZAP Express	LP013
нвха нвхв нвхс нвхр	1.5Kb	ZAF Expless	LIVIS
·IAVM	Temporal cortex-Alzheizmer	pT-Adv	LP014
AVT	Hippocampus, Alzheimer Subtracted	pT-Adv	LP014
HAS	CHME Cell Line	Uni-ZAP XR	LP014
łajr	Larynx normal	pSport 1	LP014
WLE HWLF HWLG HWLH	Colon Normal	pSport 1	LP014
ICRM HCRN HCRO	Colon Carcinoma	pSport 1	LP014
IWLI HWLJ HWLK	Colon Normal	pSport 1	LP014
HWLQ HWLR HWLS HWLT	Colon Tumor	pSport I	LP014
-IBFM	Gastrocnemius Muscle	pSport 1	LP014
HBOD HBOE	Quadriceps Muscle	pSport 1	LP014
IBKD HBKE	Soleus Muscle	pSport 1	LP014
HCCM	Pancreatic Langerhans	pSport 1	LP014
IWGA	Larynx carcinoma	pSport 1	LP014
HWGM HWGN	Larynx carcinoma	pSport 1	LP014
WLA HWLB HWLC	Normal colon	pSport 1	LP014
IWLM HWLN	Colon Tumor	pSport 1	LP014
IVAM HVAN HVAO	Pancreas Tumor	pSport 1	LP014
HWGQ	Larynx carcinoma	pSport 1	LP014
IAQM HAQN	Salivary Gland	pSport 1	LP014
IASM	Stomach; normal	pSport I	LP014
HBCM	Uterus; normal	pSport 1	LP014
ICDM	Testis; normal	pSport 1	LP014
IDJM	Brain; normal	pSport 1	LP014
IEFM	Adrenal Gland,normal	pSport 1	LP014
IBAA	Rectum normal	pSport 1	LP014
HFDM	Rectum tumour	pSport I	LP014
IGAM	Colon, normal	pSport I	LP014
IHMM	Colon, tumour	pSport I	LP014
ICLB HCLC	Human Lung Cancer	Lambda Zap II	LP015
IRLA	L1 Cell line	ZAP Express	LP015

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
ННАМ	Hypothalamus, Alzheimer's	pCMVSport 3.0	LP015
НКВА	Ku 812F Basophils Line	pSport 1	LP015
1-1525	Saos2. Dexamethosome Treated	pSport 1	LP016
HA5A	Lung Carcinoma A549 TNFalpha activated	pSport 1	LP016
НТЕМ	TF-1 Cell Line GM-CSF Treated	pSport I	LP016
HYAS	Thyroid Tumour	pSport 1	LP016
HUTS	Larynx Normal	pSport 1	LP016
HXOA	Larynx Tumor	pSport I	LP016
НЕАН	Ea.hy.926 cell line	pSport I	LP016
HINA	Adenocarcinoma Human	pSport I	LP016
HRMA	Lung Mesothelium	pSport I	LP016
HLCL	Human Pre-Differentiated Adipocytes	Uni-Zap XR	LP017
HS2A	Saos2 Cells	pSport 1	LP020
HS2I	Saos2 Cells; Vitamin D3 Treated	pSport 1	LP020
HUCM	CHME Cell Line, untreated	pSport I	LP020
HEPN	Aryepiglottis Normal	pSport 1	LP020
HPSN	Sinus Piniformis Tumour	pSport 1	LP020
HNSA	Stomach Normal	pSport 1	LP020
HNSM	Stomach Tumour	pSport I	LP020
HNLA	Liver Normal Met5No	pSport 1	LP020
HUTA	Liver Tumour Met 5 Tu	pSport 1	LP020
HOCN	Colon Normal	pSport 1	LP020
НОСТ	Colon Tumor	pSport I	LP020
HTNT	Tongue Tumour	pSport I	LP020
HLXN	Larynx Normal	pSport I	LP020
HLXT	Larynx Tumour	pSport I	LP020
HTYN	Thymus	pSport 1	LP020
HPLN	Placenta	pSport I	LP020
HTNG	Tongue Normal	pSport !	LP020
HZAA	Thyroid Normal (SDCA2 No)	pSport I	LP020
HWES	Thyroid Thyroiditis	pSport I	LP020
HFHD	Ficolled Human Stromal Cells, 5Fu	pTrip1Ex2	LP021
нғнм,нғнх	treated Ficolled Human Stromal Cells, Untreated	pTrip1Ex2	LP021
HPCI	Hep G2 Cells, lambda library	Jambda Zap-CMV XR	LP021
HBCA,HBCB,HBCC	H. Lymph node breast Cancer	Uni-ZAP XR	LP021
HCOK	Chondrocytes	pSPORT1	LP022
HDCA, HDCB, HDCC	Dendritic Cells From CD34 Cells	pSPORTI	LP022
НОМА, НОМВ	CD40 activated monocyte dendritic cells	<u> </u>	LP022
HDDM, HDDN, HDDO	LPS activated derived dendritic cells	pSPORT1	LP022
HPCR		lambda Zap-CMV XR	LP022
НАЛА, НААВ, НААС	Lung, Cancer (4005313A3): Invasive Poorly Differentiated Lung Adenocarcinoma	pSPORT1	LP022
HIPA, HIPB, HIPC		pSPORT1	LP022
100Н. НООІ	· 	pSPORT1	LP022

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
	Malignant Pot		
HIDA	Lung, Normal: (4005313 B1)	pSPORT1	LP022
HUJA.HUJB.HUJC.HUJD.HUJE	B-Cells	pCMVSport 3.0	LP022
HNOA,HNOB,HNOC,HNOD	Ovary, Normal: (9805C040R)	pSPORT1	LP022
HNLM	Lung, Normal: (4005313 B1)	pSPORT1	LP022
HSCL	Stromal Cells	pSPORT1	LP022
HAAX	Lung, Cancer: (4005313 A3) Invasive Poorly-differentiated Metastatic lung adenocarcinoma	pSPORTI	LP022
HUUA.HUUB.HUUC.HUUD	B-cells (unstimulated)	pTrip1Ex2	LP022
HWWA.HWWB.HWWC.HWWD.HW WE.HWWF.HWWG	B-cells (stimulated)	pSPORT1	LP022
HCCC	Colon, Cancer: (9808C064R)	pCMVSport 3.0	LP023
HPDO HPDP HPDQ HPDR HPD	Ovary, Cancer (9809C332): Poorly differentiated adenocarcinoma	pSport I	LP023
НРСО НРСР НРСQ НРСТ	Ovary, Cancer (15395A1F): Grade II Papillary Carcinoma	pSport 1	LP023
НОСМ НОСО НОСР НОСО	Ovary, Cancer: (15799A1F) Poorly differentiated carcinoma	pSport I	LP023
НСВМ НСВО	Breast, Cancer: (4004943 A5)	pSport I	LP023
HNBT HNBU HNBV	Breast, Normal: (4005522B2)	pSport 1	LP023
НВСР НВСQ	Breast, Cancer: (4005522 A2)	pSport I	LP023
НВСЈ	Breast, Cancer: (9806C012R)	pSport I	LP023
HSAM HSAN	Stromal cells 3.88	pSport I	LP023
HVCA HVCB HVCC HVCD	Ovary, Cancer: (4004332 A2)	pSport I	LP023
HSCK HSEN HSEO	Stromal cells (HBM3.18)	pSport I	LP023
HSCP HSCQ	stromal cell clone 2.5	pSport I	LP023
HUXA	Breast Cancer: (4005385 A2)	pSport I	LP023
НСОМ НСОО НСОР НСОО	Ovary, Cancer (4004650 A3): Well- Differentiated Micropapillary Serous Carcinoma	pSport 1	LP023
HBNM	Breast, Cancer: (9802C020E)	pSport I	LP023
HVVA HVVB HVVC HVVD HVVE	Human Bone Marrow, treated	pSport I	LP023

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 5. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to the nucleotide sequence of SEQ ID NO:X.

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Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with ³²P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the nucleotide sequence of SEQ ID NO:X are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 µl of reaction mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM MgCl₂, 0.01% (w/v) gelatin, 20 µM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not

limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

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Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the sequence corresponding to SEQ ID NO:X, according to the method described in Example 1. (See also, Sambrook.)

322

Example 3: Tissue specific expression analysis

The Human Genome Sciences, Inc. (HGS) database is derived from sequencing tissue specific cDNA libraries. Libraries generated from a particular tissue are selected and the specific tissue expression pattern of EST groups or assembled contigs within these libraries is determined by comparison of the expression patterns of those groups or contigs within the entire database. ESTs which show tissue specific expression are selected.

The original clone from which the specific EST sequence was generated, is obtained from the catalogued library of clones and the insert amplified by PCR using methods known in the art. The PCR product is denatured then transferred in 96 well format to a nylon membrane (Schleicher and Scheull) generating an array filter of tissue specific clones. Housekeeping genes, maize genes, and known tissue specific genes are included on the filters. These targets can be used in signal normalization and to validate assay sensitivity. Additional targets are included to monitor probe length and specificity of hybridization.

Radioactively labeled hybridization probes are generated by first strand cDNA synthesis per the manufacturer's instructions (Life Technologies) from mRNA/RNA samples prepared from the specific tissue being analyzed. The hybridization probes are purified by gel exclusion chromatography, quantitated, and hybridized with the array filters in hybridization bottles at 65°C overnight. The filters are washed under stringent conditions and signals are captured using a Fuji phosphorimager.

Data is extracted using AIS software and following background subtraction, signal normalization is performed. This includes a normalization of filter-wide expression levels between different experimental runs. Genes that are differentially expressed in the tissue of interest are identified and the full length sequence of these clones is generated.

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Example 4: Chromosomal Mapping of the Polynucleotides

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions: 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute

323

cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

Example 5: Bacterial Expression of a Polypeptide

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A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp^r), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan^r). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.⁶⁰⁰) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., supra). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., supra).

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Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM immidazole. Immidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4°C or frozen at -80°C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (laclq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction

sites for Ndel (5' primer) and Xbal, BamHI, Xhol, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

Example 6: Purification of a Polypeptide from an Inclusion Body

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The following alternative method can be used to purify a polypeptide expressed in *E* coli when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfuidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 µm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A₂₈₀ monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 µg of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System

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In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under

control of a weak Drosophila promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., Virology 170:31-39 (1989).

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Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon, is amplified using the PCR protocol described in Example 1. If a naturally occurring signal sequence is used to produce the polypeptide of the present invention, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("Geneclean" BIO 101 Inc., La Jolla, Ca.).

The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. E. coli HB101 or other suitable E. coli hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

Five μg of a plasmid containing the polynucleotide is co-transfected with 1.0 μg of a commercially available linearized baculovirus DNA ("BaculoGoldTM baculovirus DNA",

Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One µg of BaculoGoldTM virus DNA and 5 µg of the plasmid are mixed in a sterile well of a microtiter plate containing 50 µl of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 µl Lipofectin plus 90 µl Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

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After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 µl of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 μCi of ³⁵S-methionine and 5 μCi ³⁵S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

329

Example 8: Expression of a Polypeptide in Mammalian Cells

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The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSport 2.0, and pCMVSport 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as DHFR, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used

for the production of proteins.

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Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No.209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If a naturally occurring signal sequence is used to produce the polypeptide of the present invention, the vector does not need a second signal peptide. Alternatively, if a naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five µg of the expression plasmid pC6 or pC4 is cotransfected with 0.5 µg of the plasmid pSVneo using lipofectin (Felgner et al., supra). The plasmid pSV2-neo contains a dominant selectable marker, the neo gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10,

25, or 50 ng/ml of metothrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 μ M, 2 μ M, 5 μ M, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 μ M. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

10 Example 9: Protein Fusions

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The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the halflife time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the nonfused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the

vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the polypeptide of the present invention, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

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10 GGGATCCGGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACCGTGCCCAG CACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGA CACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGTGGTGGACGTAAGC CACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGCGTGGAGGTGCAT AATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTC 15 AGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGC AAGGTCTCCAACAAGCCCTCCCAACCCCCATCGAGAAAACCATCTCCAAAGCC AAAGGCCAGCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCGGGATGAG CTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGC GACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGAC 20 CACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACC GTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCAT GAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAT GAGTGCGACGCCGCGACTCTAGAGGAT (SEQ ID NO:837)

25 Example 10: Production of an Antibody from a Polypeptide

a) Hybridoma Technology

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The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing polypeptide of the present invention are administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of polypeptide

of the present invention is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

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Monoclonal antibodies specific for polypeptide of the present invention are prepared using hybridoma technology. (Kohler et al., Nature 256:495 (1975); Kohler et al., Eur. J. Immunol. 6:511 (1976); Kohler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with polypeptide of the present invention or, more preferably, with a secreted polypeptide of the present invention-expressing cell. Such polypeptide-expressing cells are cultured in any suitable tissue culture medium, preferably in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 μg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide of the present invention.

Alternatively, additional antibodies capable of binding to polypeptide of the present invention can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the polypeptide of the present invention-specific antibody can be blocked by polypeptide of the present invention. Such antibodies comprise anti-idiotypic antibodies to the polypeptide of the present invention-specific antibody and are used to immunize an animal to induce formation of further polypeptide of the present invention-specific antibodies.

For in vivo use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric and humanized antibodies are known in the art and are discussed herein. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

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b) Isolation Of Antibody Fragments Directed Against Polypeptide of the Present Invention From A Library Of scFvs

Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against polypeptide of the present invention to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated herein by reference in its entirety).

Rescue of the Library. A library of scFvs is constructed from the RNA of human PBLs as described in PCT publication WO 92/01047. To rescue phage displaying antibody fragments, approximately 109 E. coli harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 μg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to innoculate 50 ml of 2xTY-AMP-GLU, 2 x 108 TU of delta gene 3 helper (M13 delta gene III, see PCT publication WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 μg/ml ampicillin and 50 ug/ml kanamycin and grown overnight. Phage are prepared as described in PCT publication WO 92/01047.

M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37° C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra

8,400 r.p.m. for 10 min), resuspended in 300 ml 2xTY broth containing 100 μg ampicillin/ml and 25 μg kanamycin/ml (2xTY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 μm filter (Minisart NML; Sartorius) to give a final concentration of approximately 1013 transducing units/ml (ampicillin-resistant clones).

Panning of the Library. Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 μg/ml or 10 μg/ml of a polypeptide of the present invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times in PBS. Approximately 1013 TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1% glucose and 100 μg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

Characterization of Binders. Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 pg/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., PCT publication WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

336

Example 11: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide

RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is be isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X; and/or the nucleotide sequence of the related cDNA in the cDNA clone contained in a deposited library. Suggested PCR conditions consist of 35 cycles at 95 degrees C for 30 seconds; 60-120 seconds at 52-58 degrees C; and 60-120 seconds at 70 degrees C, using buffer solutions described in Sidransky et al., Science 252:706 (1991).

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PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

PCR products is cloned into T-tailed vectors as described in Holton et al., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Manheim), and FISH performed as described in Johnson et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image

collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

Example 12: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

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A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

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Example 13: Formulation

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The invention also provides methods of treatment and/or prevention of diseases or disorders (such as, for example, any one or more of the diseases or disorders disclosed herein) by administration to a subject of an effective amount of a Therapeutic. By therapeutic is meant a polynucleotides or polypeptides of the invention (including fragments and variants), agonists or antagonists thereof, and/or antibodies thereto, in combination with a pharmaceutically acceptable carrier type (e.g., a sterile carrier).

The Therapeutic will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the Therapeutic alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of the Therapeutic administered parenterally per dose will be in the range of about lug/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the Therapeutic is typically administered at a dose rate of about 1 ug/kg/hour to about 50 ug/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Therapeutics can be are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

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Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics include suitable polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or mirocapsules), suitable hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt).

Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., Id.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988).

Sustained-release Therapeutics also include liposomally entrapped Therapeutics of the invention (see generally, Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317 -327 and 353-365 (1989)). Liposomes containing the Therapeutic are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. (USA) 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci.(USA) 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal Therapeutic.

In yet an additional embodiment, the Therapeutics of the invention are delivered by way of a pump (see Langer, supra; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987);

Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)).

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Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

For parenteral administration, in one embodiment, the Therapeutic is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to the Therapeutic.

Generally, the formulations are prepared by contacting the Therapeutic uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The Therapeutic is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any pharmaceutical used for therapeutic administration can be sterile. Sterility is

341

readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutics generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

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Therapeutics ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous Therapeutic solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized Therapeutic using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the Therapeutics of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the Therapeutics may be employed in conjunction with other therapeutic compounds.

The Therapeutics of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG, and MPL. In a specific embodiment, Therapeutics of the invention are administered in combination with alum. In another specific embodiment, Therapeutics of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the Therapeutics of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diptheria, hepatitis A, hepatitis B, haemophilus influenzae B, whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or

concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

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The Therapeutics of the invention may be administered alone or in combination with other therapeutic agents. Therapeutic agents that may be administered in combination with the Therapeutics of the invention, include but not limited to, other members of the TNF family, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents, cytokines and/or growth factors. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

In one embodiment, the Therapeutics of the invention are administered in combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the Therapeutics of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880); TR6 (International Publication No. WO 98/30694), OPG, and neutrokine-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

In certain embodiments, Therapeutics of the invention are administered in combination with antiretroviral agents, nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and/or protease inhibitors. Nucleoside reverse transcriptase inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). Non-nucleoside reverse transcriptase inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delayirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, CRIXIVAN™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with Therapeutics of the invention to treat AIDS and/or to prevent or treat HIV infection.

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In other embodiments, Therapeutics of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the Therapeutics of the invention, include, but are not TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, limited PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICOLVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, Therapeutics of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™. DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic Pneumocystis carinii pneumonia infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or

344

prevent an opportunistic Mycobacterium avium complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or prevent an opportunistic Mycobacterium tuberculosis infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific embodiment, Therapeutics of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, Therapeutics of the invention are used in any combination with PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an opportunistic Toxoplasma gondii infection. In another specific embodiment, Therapeutics of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial infection.

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In a further embodiment, the Therapeutics of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the Therapeutics of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

In a further embodiment, the Therapeutics of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the Therapeutics of the invention include, but are not limited to, amoxicillin, beta-lactamases, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamthoxazole, and vancomycin.

Conventional nonspecific immunosuppressive agents, that may be administered in combination with the Therapeutics of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone,

azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells.

In specific embodiments, Therapeutics of the invention are administered in combination with immunosuppressants. Immunosuppressants preparations that may be administered with the Therapeutics of the invention include, but are not limited to, ORTHOCLONE™ (OKT3), SANDIMMUNE™/NEORAL™/SANGDYA™ (cyclosporin), PROGRAF™ (tacrolimus), CELLCEPT™ (mycophenolate), Azathioprine, glucorticosteroids, and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

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In an additional embodiment, Therapeutics of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the Therapeutics of the invention include, but not limited to, GAMMARTM, IVEEGAMTM, SANDOGLOBULINTM, GAMMAGARD S/DTM, and GAMIMUNETM. In a specific embodiment, Therapeutics of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

In an additional embodiment, the Therapeutics of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the Therapeutics of the invention include, but are not limited to, glucocorticoids and the nonsteroidal anti-inflammatories, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

In another embodiment, compostions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the Therapeutics of the invention include, but are not limited to, antibiotic derivatives (e.g., doxorubicin, bleomycin, daunorubicin, and dactinomycin); antiestrogens (e.g., tamoxifen); antimetabolites (e.g., fluorouracil, 5-FU, methotrexate, floxuridine, interferon alpha-2b, glutamic acid, plicamycin, mercaptopurine, and 6-thioguanine);

cyclophosphamide, estramustine, hydroxyurea, procarbazine, mitomycin, busulfan, cis-platin, and vincristine sulfate); hormones (e.g., medroxyprogesterone, estramustine phosphate sodium, ethinyl estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol diphosphate, chlorotrianisene, and testolactone); nitrogen mustard derivatives (e.g., mephalen, chorambucil, mechlorethamine (nitrogen mustard) and thiotepa); steroids and combinations (e.g., bethamethasone sodium phosphate); and others (e.g., dicarbazine, asparaginase, mitotane, vincristine sulfate, vinblastine sulfate, and etoposide).

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In a specific embodiment, Therapeutics of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or any combination of the components of CHOP. In another embodiment, Therapeutics of the invention are administered in combination with Rituximab. In a further embodiment, Therapeutics of the invention are administered with Rituximab and CHOP, or Rituxmab and any combination of the components of CHOP.

In an additional embodiment, the Therapeutics of the invention are administered in combination with cytokines. Cytokines that may be administered with the Therapeutics of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment, Therapeutics of the invention may be administered with any interleukin, including, but not limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

In an additional embodiment, the Therapeutics of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the Therapeutics of the invention include, but are not limited to, Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PIGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PIGF-2), as disclosed in Hauser et al., Gorwth Factors, 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2

(VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are incorporated herein by reference herein.

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In an additional embodiment, the Therapeutics of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the Therapeutics of the invention include, but are not limited to, LEUKINE[™] (SARGRAMOSTIM[™]) and NEUPOGEN[™] (FILGRASTIM[™]).

In an additional embodiment, the Therapeutics of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the Therapeutics of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

In additional embodiments, the Therapeutics of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

Example 14: Method of Treating Decreased Levels of the Polypeptide

The present invention relates to a method for treating an individual in need of an increased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an agonist of the invention (including polypeptides of the invention). Moreover, it will be appreciated that conditions caused by a decrease in the standard or normal expression level of a polypeptide of the present invention in an individual can be treated by administering the agonist or antagonist of the present invention. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a Therapeutic comprising an amount of the agonist or

348

antagonist to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the agonist or antagonist for six consecutive days. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 13.

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Example 15: Method of Treating Increased Levels of the Polypeptide

The present invention also relates to a method of treating an individual in need of a decreased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an antagonist of the invention (including polypeptides and antibodies of the invention).

In one example, antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, due to a variety of etiologies, such as cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 13.

Example 16: Method of Treatment Using Gene Therapy-Ex Vivo

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37 degree C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

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pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1 using primers and having appropriate restriction sites and initiation/stop codons, if necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a subconfluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after

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having been grown to confluence on cytodex 3 microcarrier beads.

Example 17: Gene Therapy Using Endogenous Genes Corresponding To Polynucleotides of the Invention

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Another method of gene therapy according to the present invention involves operably associating the endogenous polynucleotide sequence of the invention with a promoter via homologous recombination as described, for example, in U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., *Proc. Natl. Acad. Sci. USA*, 86:8932-8935 (1989); and Zijlstra et al., *Nature*, 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made which contain a promoter and targeting sequences, which are homologous to the 5' non-coding sequence of endogenous polynucleotide sequence, flanking the promoter. The targeting sequence will be sufficiently near the 5' end of the polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter.

The amplified promoter and the amplified targeting sequences are digested with the appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added together in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel then purified by phenol extraction and ethanol precipitation.

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In this Example, the polynucleotide constructs are administered as naked polynucleotides via electroporation. However, the polynucleotide constructs may also be administered with transfection-facilitating agents, such as liposomes, viral sequences, viral

351

particles, precipitating agents, etc. Such methods of delivery are known in the art.

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Once the cells are transfected, homologous recombination will take place which results in the promoter being operably linked to the endogenous polynucleotide sequence. This results in the expression of polynucleotide corresponding to the polynucleotide in the cell. Expression may be detected by immunological staining, or any other method known in the art.

Fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in DMEM + 10% fetal calf serum. Exponentially growing or early stationary phase fibroblasts are trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining cells are subjected to centrifugation. The supernatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM Na₂ HPO₄, 6 mM dextrose). The cells are recentrifuged, the supernatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin. The final cell suspension contains approximately 3X10⁶ cells/ml. Electroporation should be performed immediately following resuspension.

Plasmid DNA is prepared according to standard techniques. For example, to construct a plasmid for targeting to the locus corresponding to the polynucleotide of the invention, plasmid pUC18 (MBI Fermentas, Amherst, NY) is digested with HindIII. The CMV promoter is amplified by PCR with an XbaI site on the 5' end and a BamHI site on the 3'end. Two non-coding sequences are amplified via PCR: one non-coding sequence (fragment 1) is amplified with a HindIII site at the 5' end and an Xba site at the 3'end; the other non-coding sequence (fragment 2) is amplified with a BamHI site at the 5'end and a HindIII site at the 3'end. The CMV promoter and the fragments (1 and 2) are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; fragment 1 - XbaI; fragment 2 - BamHI) and ligated together. The resulting ligation product is digested with HindIII, and ligated with the HindIII-digested pUC18 plasmid.

Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap (Bio-Rad). The final DNA concentration is generally at least $120 \,\mu\text{g/ml}$. 0.5 ml of the cell suspension (containing approximately $1.5.X10^6$ cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at 960 μF and 250-300 V,

respectively. As voltage increases, cell survival decreases, but the percentage of surviving cells that stably incorporate the introduced DNA into their genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

Electroporated cells are maintained at room temperature for approximately 5 min, and the contents of the cuvette are then gently removed with a sterile transfer pipette. The cells are added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a 10 cm dish and incubated at 37 degree C. The following day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.

The engineered fibroblasts are then injected into the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a patient as described above.

Example 18: Method of Treatment Using Gene Therapy - In Vivo

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Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata et al., Cardiovasc. Res. 35(3):470-479 (1997); Chao et al., Pharmacol. Res. 35(6):517-522 (1997); Wolff, Neuromuscul. Disord. 7(5):314-318 (1997); Schwartz et al., Gene Ther. 3(5):405-411 (1996); Tsurumi et al., Circulation 94(12):3281-3290 (1996) (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell,

including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

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The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will

354

appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

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The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, e.g., baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (i.e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e.g., Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pleuripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

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Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.*, mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci.

USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, in situ hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

357

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

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Example 20: Knock-Out Animals

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (E.g., see Smithies et al., Nature 317:230-234 (1985); Thomas & Capecchi, Cell 51:503-512 (1987); Thompson et al., Cell 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention in vivo. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (e.g., see Thomas & Capecchi 1987 and Thompson 1989, supra). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site in vivo using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (e.g., knockouts) are administered to a patient in vivo. Such cells may be obtained from the patient (i.e., animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (e.g., lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered in vitro using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e.g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e.g., in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, e.g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Example 22: Assays Detecting Stimulation or Inhibition of B cell Proliferation and Differentiation

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Generation of functional humoral immune responses requires both soluble and cognate signaling between B-lineage cells and their microenvironment. Signals may impart a

positive stimulus that allows a B-lineage cell to continue its programmed development, or a negative stimulus that instructs the cell to arrest its current developmental pathway. To date, numerous stimulatory and inhibitory signals have been found to influence B cell responsiveness including IL-2, IL-4, IL-5, IL-6, IL-7, IL10, IL-13, IL-14 and IL-15. Interestingly, these signals are by themselves weak effectors but can, in combination with various co-stimulatory proteins, induce activation, proliferation, differentiation, homing, tolerance and death among B cell populations.

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One of the best studied classes of B-cell co-stimulatory proteins is the TNF-superfamily. Within this family CD40, CD27, and CD30 along with their respective ligands CD154, CD70, and CD153 have been found to regulate a variety of immune responses. Assays which allow for the detection and/or observation of the proliferation and differentiation of these B-cell populations and their precursors are valuable tools in determining the effects various proteins may have on these B-cell populations in terms of proliferation and differentiation. Listed below are two assays designed to allow for the detection of the differentiation, proliferation, or inhibition of B-cell populations and their precursors.

In Vitro Assay- Agonists or antagonists of the invention can be assessed for its ability to induce activation, proliferation, differentiation or inhibition and/or death in B-cell populations and their precursors. The activity of the agonists or antagonists of the invention on purified human tonsillar B cells, measured qualitatively over the dose range from 0.1 to 10,000 ng/mL, is assessed in a standard B-lymphocyte co-stimulation assay in which purified tonsillar B cells are cultured in the presence of either formalin-fixed Staphylococcus aureus Cowan I (SAC) or immobilized anti-human IgM antibody as the priming agent. Second signals such as IL-2 and IL-15 synergize with SAC and IgM crosslinking to elicit B cell proliferation as measured by tritiated-thymidine incorporation. Novel synergizing agents can be readily identified using this assay. The assay involves isolating human tonsillar B cells by magnetic bead (MACS) depletion of CD3-positive cells. The resulting cell population is greater than 95% B cells as assessed by expression of CD45R(B220).

Various dilutions of each sample are placed into individual wells of a 96-well plate to which are added 10⁵ B-cells suspended in culture medium (RPMI 1640 containing 10% FBS, 5 X 10⁻⁵M 2ME, 100U/ml penicillin, 10ug/ml streptomycin, and 10⁻⁵ dilution of SAC) in a total volume of 150ul. Proliferation or inhibition is quantitated by a 20h pulse (1uCi/well)

with 3H-thymidine (6.7 Ci/mM) beginning 72h post factor addition. The positive and negative controls are IL2 and medium respectively.

In Vivo Assay- BALB/c mice are injected (i.p.) twice per day with buffer only, or 2 mg/Kg of agonists or antagonists of the invention, or truncated forms thereof. Mice receive this treatment for 4 consecutive days, at which time they are sacrificed and various tissues and serum collected for analyses. Comparison of H&E sections from normal spleens and spleens treated with agonists or antagonists of the invention identify the results of the activity of the agonists or antagonists on spleen cells, such as the diffusion of peri-arterial lymphatic sheaths, and/or significant increases in the nucleated cellularity of the red pulp regions, which may indicate the activation of the differentiation and proliferation of B-cell populations. Immunohistochemical studies using a B cell marker, anti-CD45R(B220), are used to determine whether any physiological changes to splenic cells, such as splenic disorganization, are due to increased B-cell representation within loosely defined B-cell zones that infiltrate established T-cell regions.

Flow cytometric analyses of the spleens from mice treated with agonist or antagonist is used to indicate whether the agonists or antagonists specifically increases the proportion of ThB+, CD45R(B220)dull B cells over that which is observed in control mice.

Likewise, a predicted consequence of increased mature B-cell representation in vivo is a relative increase in serum Ig titers. Accordingly, serum IgM and IgA levels are compared between buffer and agonists or antagonists-treated mice.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 23: T Cell Proliferation Assay

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A CD3-induced proliferation assay is performed on PBMCs and is measured by the uptake of ³H-thymidine. The assay is performed as follows. Ninety-six well plates are coated with 100 µl/well of mAb to CD3 (HIT3a, Pharmingen) or isotype-matched control mAb (B33.1) overnight at 4 degrees C (1 µg/ml in .05M bicarbonate buffer, pH 9.5), then washed three times with PBS. PBMC are isolated by F/H gradient centrifugation from human peripheral blood and added to quadruplicate wells (5 x 10⁴/well) of mAb coated plates

in RPMI containing 10% FCS and P/S in the presence of varying concentrations of agonists or antagonists of the invention (total volume 200 ul). Relevant protein buffer and medium alone are controls. After 48 hr. culture at 37 degrees C, plates are spun for 2 min. at 1000 rpm and 100 µl of supernatant is removed and stored –20 degrees C for measurement of IL-2 (or other cytokines) if effect on proliferation is observed. Wells are supplemented with 100 ul of medium containing 0.5 uCi of ³H-thymidine and cultured at 37 degrees C for 18-24 hr. Wells are harvested and incorporation of ³H-thymidine used as a measure of proliferation. Anti-CD3 alone is the positive control for proliferation. IL-2 (100 U/ml) is also used as a control which enhances proliferation. Control antibody which does not induce proliferation of T cells is used as the negative controls for the effects of agonists or antagonists of the invention.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

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Example 24: Effect of Agonists or Antagonists of the Invention on the Expression of MHC Class II, Costimulatory and Adhesion Molecules and Cell Differentiation of Monocytes and Monocyte-Derived Human Dendritic Cells

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Dendritic cells are generated by the expansion of proliferating precursors found in the peripheral blood: adherent PBMC or elutriated monocytic fractions are cultured for 7-10 days with GM-CSF (50 ng/ml) and IL-4 (20 ng/ml). These dendritic cells have the characteristic phenotype of immature cells (expression of CD1, CD80, CD86, CD40 and MHC class II antigens). Treatment with activating factors, such as TNF-α, causes a rapid change in surface phenotype (increased expression of MHC class I and II, costimulatory and adhesion molecules, downregulation of FCγRII, upregulation of CD83). These changes correlate with increased antigen-presenting capacity and with functional maturation of the dendritic cells.

FACS analysis of surface antigens is performed as follows. Cells are treated 1-3 days with increasing concentrations of agonist or antagonist of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow

362

cytometry on a FACScan (Becton Dickinson).

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Effect on the production of cytokines. Cytokines generated by dendritic cells, in particular IL-12, are important in the initiation of T-cell dependent immune responses. IL-12 strongly influences the development of Thl helper T-cell immune response, and induces cytotoxic T and NK cell function. An ELISA is used to measure the IL-12 release as follows. Dendritic cells (10⁶/ml) are treated with increasing concentrations of agonists or antagonists of the invention for 24 hours. LPS (100 ng/ml) is added to the cell culture as positive control. Supernatants from the cell cultures are then collected and analyzed for IL-12 content using commercial ELISA kit (e..g, R & D Systems (Minneapolis, MN)). The standard protocols provided with the kits are used.

Effect on the expression of MHC Class II, costimulatory and adhesion molecules. Three major families of cell surface antigens can be identified on monocytes: adhesion molecules, molecules involved in antigen presentation, and Fc receptor. Modulation of the expression of MHC class II antigens and other costimulatory molecules, such as B7 and ICAM-1, may result in changes in the antigen presenting capacity of monocytes and ability to induce T cell activation. Increase expression of Fc receptors may correlate with improved monocyte cytotoxic activity, cytokine release and phagocytosis.

FACS analysis is used to examine the surface antigens as follows. Monocytes are treated 1-5 days with increasing concentrations of agonists or antagonists of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degreesC. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

Monocyte activation and/or increased survival. Assays for molecules that activate (or alternatively, inactivate) monocytes and/or increase monocyte survival (or alternatively, decrease monocyte survival) are known in the art and may routinely be applied to determine whether a molecule of the invention functions as an inhibitor or activator of monocytes. Agonists or antagonists of the invention can be screened using the three assays described below. For each of these assays, Peripheral blood mononuclear cells (PBMC) are purified

363

from single donor leukopacks (American Red Cross, Baltimore, MD) by centrifugation through a Histopaque gradient (Sigma). Monocytes are isolated from PBMC by counterflow centrifugal elutriation.

Monocyte Survival Assay. Human peripheral blood monocytes progressively lose viability 5 when cultured in absence of serum or other stimuli. Their death results from internally regulated process (apoptosis). Addition to the culture of activating factors, such as TNF-alpha dramatically improves cell survival and prevents DNA fragmentation. Propidium iodide (PI) staining is used to measure apoptosis as follows. Monocytes are cultured for 48 hours in 10 polypropylene tubes in serum-free medium (positive control), in the presence of 100 ng/ml TNF-alpha (negative control), and in the presence of varying concentrations of the compound to be tested. Cells are suspended at a concentration of 2 x 10⁶/ml in PBS containing PI at a final concentration of 5 µg/ml, and then incubaed at room temperature for 5 minutes before FACScan analysis. PI uptake has been demonstrated to correlate with DNA fragmentation in this experimental paradigm.

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Effect on cytokine release. An important function of monocytes/macrophages is their regulatory activity on other cellular populations of the immune system through the release of cytokines after stimulation. An ELISA to measure cytokine release is performed as follows. Human monocytes are incubated at a density of 5×10^5 cells/ml with increasing concentrations of agonists or antagonists of the invention and under the same conditions, but in the absence of agonists or antagonists. For IL-12 production, the cells are primed overnight with IFN (100 U/ml) in presence of agonist or antagonist of the invention. LPS (10 ng/ml) is then added. Conditioned media are collected after 24h and kept frozen until use. Measurement of TNF-alpha, IL-10, MCP-1 and IL-8 is then performed using a commercially available ELISA kit (e. g, R & D Systems (Minneapolis, MN)) and applying the standard. protocols provided with the kit.

Oxidative burst. Purified monocytes are plated in 96-w plate at 2-1x10⁵ cell/well. Increasing concentrations of agonists or antagonists of the invention are added to the wells in a total volume of 0.2 ml culture medium (RPMI 1640 + 10% FCS, glutamine and antibiotics). After 3 days incubation, the plates are centrifuged and the medium is removed from the wells. To the macrophage monolayers, 0.2 ml per well of phenol red solution (140 mM NaCl, 10 mM potassium phosphate buffer pH 7.0, 5.5 mM dextrose, 0.56 mM phenol red and 19 U/ml of HRPO) is added, together with the stimulant (200 nM PMA). The plates are incubated at 37°C for 2 hours and the reaction is stopped by adding 20 μ l 1N NaOH per well. The absorbance is read at 610 nm. To calculate the amount of H_2O_2 produced by the macrophages, a standard curve of a H_2O_2 solution of known molarity is performed for each experiment.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 25: Biological Effects of Agonists or Antagonists of the Invention

15 Astrocyte and Neuronal Assays.

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Agonists or antagonists of the invention, expressed in *Escherichia coli* and purified as described above, can be tested for activity in promoting the survival, neurite outgrowth, or phenotypic differentiation of cortical neuronal cells and for inducing the proliferation of glial fibrillary acidic protein immunopositive cells, astrocytes. The selection of cortical cells for the bioassay is based on the prevalent expression of FGF-1 and FGF-2 in cortical structures and on the previously reported enhancement of cortical neuronal survival resulting from FGF-2 treatment. A thymidine incorporation assay, for example, can be used to elucidate an agonist or antagonist of the invention's activity on these cells.

Moreover, previous reports describing the biological effects of FGF-2 (basic FGF) on cortical or hippocampal neurons *in vitro* have demonstrated increases in both neuron survival and neurite outgrowth (Walicke et al., "Fibroblast growth factor promotes survival of dissociated hippocampal neurons and enhances neurite extension." *Proc. Natl. Acad. Sci. USA 83*:3012-3016. (1986), assay herein incorporated by reference in its entirety). However, reports from experiments done on PC-12 cells suggest that these two responses are not necessarily synonymous and may depend on not only which FGF is being tested but also on which receptor(s) are expressed on the target cells. Using the primary cortical neuronal

culture paradigm, the ability of an agonist or antagonist of the invention to induce neurite outgrowth can be compared to the response achieved with FGF-2 using, for example, a thymidine incorporation assay.

5 Fibroblast and endothelial cell assays.

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Human lung fibroblasts are obtained from Clonetics (San Diego, CA) and maintained in growth media from Clonetics. Dermal microvascular endothelial cells are obtained from Cell Applications (San Diego, CA). For proliferation assays, the human lung fibroblasts and dermal microvascular endothelial cells can be cultured at 5,000 cells/well in a 96-well plate for one day in growth medium. The cells are then incubated for one day in 0.1% BSA basal medium. After replacing the medium with fresh 0.1% BSA medium, the cells are incubated with the test proteins for 3 days. Alamar Blue (Alamar Biosciences, Sacramento, CA) is added to each well to a final concentration of 10%. The cells are incubated for 4 hr. Cell viability is measured by reading in a CytoFluor fluorescence reader. For the PGE2 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or agonists or antagonists of the invention with or without IL-1\alpha for 24 hours. The supernatants are collected and assayed for PGE₂ by EIA kit (Cayman, Ann Arbor, MI). For the IL-6 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or with or without agonists or antagonists of the invention IL-1a for 24 hours. The supernatants are collected and assayed for IL-6 by ELISA kit (Endogen, Cambridge, MA).

Human lung fibroblasts are cultured with FGF-2 or agonists or antagonists of the invention for 3 days in basal medium before the addition of Alamar Blue to assess effects on growth of the fibroblasts. FGF-2 should show a stimulation at 10 - 2500 ng/ml which can be used to compare stimulation with agonists or antagonists of the invention.

Parkinson Models.

The loss of motor function in Parkinson's disease is attributed to a deficiency of striatal dopamine resulting from the degeneration of the nigrostriatal dopaminergic projection

neurons. An animal model for Parkinson's that has been extensively characterized involves the systemic administration of 1-methyl-4 phenyl 1,2,3,6-tetrahydropyridine (MPTP). In the CNS, MPTP is taken-up by astrocytes and catabolized by monoamine oxidase B to 1-methyl-4-phenyl pyridine (MPP⁺) and released. Subsequently, MPP⁺ is actively accumulated in dopaminergic neurons by the high-affinity reuptake transporter for dopamine. MPP⁺ is then concentrated in mitochondria by the electrochemical gradient and selectively inhibits nicotidamide adenine disphosphate: ubiquinone oxidoreductionase (complex I), thereby interfering with electron transport and eventually generating oxygen radicals.

It has been demonstrated in tissue culture paradigms that FGF-2 (basic FGF) has trophic activity towards nigral dopaminergic neurons (Ferrari et al., Dev. Biol. 1989). Recently, Dr. Unsicker's group has demonstrated that administering FGF-2 in gel foam implants in the striatum results in the near complete protection of nigral dopaminergic neurons from the toxicity associated with MPTP exposure (Otto and Unsicker, J. Neuroscience, 1990).

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Based on the data with FGF-2, agonists or antagonists of the invention can be evaluated to determine whether it has an action similar to that of FGF-2 in enhancing dopaminergic neuronal survival in vitro and it can also be tested in vivo for protection of dopaminergic neurons in the striatum from the damage associated with MPTP treatment. The potential effect of an agonist or antagonist of the invention is first examined in vitro in a dopaminergic neuronal cell culture paradigm. The cultures are prepared by dissecting the midbrain floor plate from gestation day 14 Wistar rat embryos. The tissue is dissociated with trypsin and seeded at a density of 200,000 cells/cm² on polyorthinine-laminin coated glass coverslips. The cells are maintained in Dulbecco's Modified Eagle's medium and F12 medium containing hormonal supplements (N1). The cultures are fixed with paraformaldehyde after 8 days in vitro and are processed for tyrosine hydroxylase, a specific marker for dopminergic neurons, immunohistochemical staining. Dissociated cell cultures are prepared from embryonic rats. The culture medium is changed every third day and the factors are also added at that time.

Since the dopaminergic neurons are isolated from animals at gestation day 14, a developmental time which is past the stage when the dopaminergic precursor cells are proliferating, an increase in the number of tyrosine hydroxylase immunopositive neurons would represent an increase in the number of dopaminergic neurons surviving in vitro.

Therefore, if an agonist or antagonist of the invention acts to prolong the survival of dopaminergic neurons, it would suggest that the agonist or antagonist may be involved in Parkinson's Disease.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 26: The Effect of Agonists or Antagonists of the Invention on the Growth of Vascular Endothelial Cells

On day 1, human umbilical vein endothelial cells (HUVEC) are seeded at 2-5x10⁴ cells/35 mm dish density in M199 medium containing 4% fetal bovine serum (FBS), 16 units/ml heparin, and 50 units/ml endothelial cell growth supplements (ECGS, Biotechnique, Inc.). On day 2, the medium is replaced with M199 containing 10% FBS, 8 units/ml heparin. An agonist or antagonist of the invention, and positive controls, such as VEGF and basic FGF (bFGF) are added, at varying concentrations. On days 4 and 6, the medium is replaced. On day 8, cell number is determined with a Coulter Counter.

An increase in the number of HUVEC cells indicates that the compound of the invention may proliferate vascular endothelial cells, while a decrease in the number of HUVEC cell indicates that the compound of the invention inhibits vascular endothelial cells.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 27: Rat Corneal Wound Healing Model

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This animal model shows the effect of an agonist or antagonist of the invention on neovascularization. The experimental protocol includes:

- a) Making a 1-1.5 mm long incision from the center of comea into the stromal layer.
 - b) Inserting a spatula below the lip of the incision facing the outer corner of the

eye.

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- c) Making a pocket (its base is 1-1.5 mm form the edge of the eye).
- d) Positioning a pellet, containing 50ng- 5ug of an agonist or antagonist of the invention, within the pocket.
- e) Treatment with an agonist or antagonist of the invention can also be applied topically to the corneal wounds in a dosage range of 20mg 500mg (daily treatment for five days).

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 28: Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models

A. Diabetic db+/db+ Mouse Model.

To demonstrate that an agonist or antagonist of the invention accelerates the healing process, the genetically diabetic mouse model of wound healing is used. The full thickness wound healing model in the db+/db+ mouse is a well characterized, clinically relevant and reproducible model of impaired wound healing. Healing of the diabetic wound is dependent on formation of granulation tissue and re-epithelialization rather than contraction (Gartner, M.H. et al., J. Surg. Res. 52:389 (1992); Greenhalgh, D.G. et al., Am. J. Pathol. 136:1235 (1990)).

The diabetic animals have many of the characteristic features observed in Type II diabetes mellitus. Homozygous (db+/db+) mice are obese in comparison to their normal heterozygous (db+/+m) littermates. Mutant diabetic (db+/db+) mice have a single autosomal recessive mutation on chromosome 4 (db+) (Coleman et al. Proc. Natl. Acad. Sci. USA 77:283-293 (1982)). Animals show polyphagia, polydipsia and polyuria. Mutant diabetic mice (db+/db+) have elevated blood glucose, increased or normal insulin levels, and suppressed cell-mediated immunity (Mandel et al., J. Immunol. 120:1375 (1978); Debray-Sachs, M. et al., Clin. Exp. Immunol. 51(1):1-7 (1983); Leiter et al., Am. J. of Pathol. 114:46-55 (1985)). Peripheral neuropathy, myocardial complications, and microvascular lesions, basement membrane thickening and glomerular filtration abnormalities have been described in these animals (Norido, F. et al., Exp. Neurol. 83(2):221-232 (1984); Robertson et al.,

Diabetes 29(1):60-67 (1980); Giacomelli et al., Lab Invest. 40(4):460-473 (1979); Coleman, D.L., Diabetes 31 (Suppl):1-6 (1982)). These homozygous diabetic mice develop hyperglycemia that is resistant to insulin analogous to human type II diabetes (Mandel et al., J. Immunol. 120:1375-1377 (1978)).

The characteristics observed in these animals suggests that healing in this model may be similar to the healing observed in human diabetes (Greenhalgh, et al., Am. J. of Pathol. 136:1235-1246 (1990)).

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Genetically diabetic female C57BL/KsJ (db+/db+) mice and their non-diabetic (db+/+m) heterozygous littermates are used in this study (Jackson Laboratories). The animals are purchased at 6 weeks of age and are 8 weeks old at the beginning of the study. Animals are individually housed and received food and water ad libitum. All manipulations are performed using aseptic techniques. The experiments are conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

Wounding protocol is performed according to previously reported methods (Tsuboi, R. and Rifkin, D.B., J. Exp. Med. 172:245-251 (1990)). Briefly, on the day of wounding, animals are anesthetized with an intraperitoneal injection of Avertin (0.01 mg/mL), 2,2,2-tribromoethanol and 2-methyl-2-butanol dissolved in deionized water. The dorsal region of the animal is shaved and the skin washed with 70% ethanol solution and iodine. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is then created using a Keyes tissue punch. Immediately following wounding, the surrounding skin is gently stretched to eliminate wound expansion. The wounds are left open for the duration of the experiment. Application of the treatment is given topically for 5 consecutive days commencing on the day of wounding. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of surgery and at two day intervals thereafter. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

An agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups

received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology and immunohistochemistry. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

Three groups of 10 animals each (5 diabetic and 5 non-diabetic controls) are evaluated: 1) Vehicle placebo control, 2) untreated group, and 3) treated group.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total square area of the wound. Contraction is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm², the corresponding size of the dermal punch. Calculations are made using the following formula:

[Open area on day 8] - [Open area on day 1] / [Open area on day 1]

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Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using a Reichert-Jung microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds are used to assess whether the healing process and the morphologic appearance of the repaired skin is altered by treatment with an agonist or antagonist of the invention. This assessment included verification of the presence of cell accumulation, inflammatory cells, capillaries, fibroblasts, re-epithelialization and epidermal maturity (Greenhalgh, D.G. et al., Am. J. Pathol. 136:1235 (1990)). A calibrated lens micrometer is used by a blinded observer.

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Tissue sections are also stained immunohistochemically with a polyclonal rabbit antihuman keratin antibody using ABC Elite detection system. Human skin is used as a positive tissue control while non-immune IgG is used as a negative control. Keratinocyte growth is determined by evaluating the extent of reepithelialization of the wound using a calibrated lens micrometer.

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Proliferating cell nuclear antigen/cyclin (PCNA) in skin specimens is demonstrated by using anti-PCNA antibody (1:50) with an ABC Elite detection system. Human colon cancer served as a positive tissue control and human brain tissue is used as a negative tissue

371

control. Each specimen included a section with omission of the primary antibody and substitution with non-immune mouse IgG. Ranking of these sections is based on the extent of proliferation on a scale of 0-8, the lower side of the scale reflecting slight proliferation to the higher side reflecting intense proliferation.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

B. Steroid Impaired Rat Model

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The inhibition of wound healing by steroids has been well documented in various in vitro and in vivo systems (Wahl, Glucocorticoids and Wound healing. In: Anti-Inflammatory Steroid Action: Basic and Clinical Aspects. 280-302 (1989); Wahlet al., J. Immunol. 115: 476-481 (1975); Werb et al., J. Exp. Med. 147:1684-1694 (1978)). Glucocorticoids retard wound healing by inhibiting angiogenesis, decreasing vascular permeability (Ebert et al., An. Intern. Med. 37:701-705 (1952)), fibroblast proliferation, and collagen synthesis (Beck et al., Growth Factors. 5: 295-304 (1991); Haynes et al., J. Clin. Invest. 61: 703-797 (1978)) and producing a transient reduction of circulating monocytes (Haynes et al., J. Clin. Invest. 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989)). The systemic administration of steroids to impaired wound healing is a well establish phenomenon in rats (Beck et al., Growth Factors. 5: 295-304 (1991); Haynes et al., J. Clin. Invest. 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989); Pierce et al., Proc. Natl. Acad. Sci. USA 86: 2229-2233 (1989)).

To demonstrate that an agonist or antagonist of the invention can accelerate the healing process, the effects of multiple topical applications of the agonist or antagonist on full thickness excisional skin wounds in rats in which healing has been impaired by the systemic administration of methylprednisolone is assessed.

Young adult male Sprague Dawley rats weighing 250-300 g (Charles River Laboratories) are used in this example. The animals are purchased at 8 weeks of age and are 9 weeks old at the beginning of the study. The healing response of rats is impaired by the systemic administration of methylprednisolone (17mg/kg/rat intramuscularly) at the time of wounding. Animals are individually housed and received food and water *ad libitum*. All

manipulations are performed using aseptic techniques. This study is conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

The wounding protocol is followed according to section A, above. On the day of wounding, animals are anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). The dorsal region of the animal is shaved and the skin washed with 70% ethanol and iodine solutions. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is created using a Keyes tissue punch. The wounds are left open for the duration of the experiment. Applications of the testing materials are given topically once a day for 7 consecutive days commencing on the day of wounding and subsequent to methylprednisolone administration. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

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Wounds are visually examined and photographed at a fixed distance at the day of wounding and at the end of treatment. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

The agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

Four groups of 10 animals each (5 with methylprednisolone and 5 without glucocorticoid) are evaluated: 1) Untreated group 2) Vehicle placebo control 3) treated groups.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total area of the wound. Closure is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm², the corresponding size of the dermal punch. Calculations are made using the following formula:

[Open area on day 8] - [Open area on day 1] / [Open area on day 1]

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using an Olympus microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds allows assessment of whether the healing process and the morphologic appearance of the repaired skin is improved by treatment with an agonist or antagonist of the invention. A calibrated lens micrometer is used by a blinded observer to determine the distance of the wound gap.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 29: Lymphadema Animal Model

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The purpose of this experimental approach is to create an appropriate and consistent lymphedema model for testing the therapeutic effects of an agonist or antagonist of the invention in lymphangiogenesis and re-establishment of the lymphatic circulatory system in the rat hind limb. Effectiveness is measured by swelling volume of the affected limb, quantification of the amount of lymphatic vasculature, total blood plasma protein, and histopathology. Acute lymphedema is observed for 7-10 days. Perhaps more importantly, the chronic progress of the edema is followed for up to 3-4 weeks.

Prior to beginning surgery, blood sample is drawn for protein concentration analysis. Male rats weighing approximately ~350g are dosed with Pentobarbital. Subsequently, the right legs are shaved from knee to hip. The shaved area is swabbed with gauze soaked in 70% EtOH. Blood is drawn for serum total protein testing. Circumference and volumetric measurements are made prior to injecting dye into paws after marking 2 measurement levels (0.5 cm above heel, at mid-pt of dorsal paw). The intradermal dorsum of both right and left paws are injected with 0.05 ml of 1% Evan's Blue. Circumference and volumetric

374

measurements are then made following injection of dye into paws.

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Using the knee joint as a landmark, a mid-leg inguinal incision is made circumferentially allowing the femoral vessels to be located. Forceps and hemostats are used to dissect and separate the skin flaps. After locating the femoral vessels, the lymphatic vessel that runs along side and underneath the vessel(s) is located. The main lymphatic vessels in this area are then electrically coagulated or suture ligated.

Using a microscope, muscles in back of the leg (near the semitendinosis and adductors) are bluntly dissected. The popliteal lymph node is then located. The 2 proximal and 2 distal lymphatic vessels and distal blood supply of the popliteal node are then and ligated by suturing. The popliteal lymph node, and any accompanying adipose tissue, is then removed by cutting connective tissues.

Care is taken to control any mild bleeding resulting from this procedure. After lymphatics are occluded, the skin flaps are sealed by using liquid skin (Vetbond) (AJ Buck). The separated skin edges are sealed to the underlying muscle tissue while leaving a gap of ~0.5 cm around the leg. Skin also may be anchored by suturing to underlying muscle when necessary.

To avoid infection, animals are housed individually with mesh (no bedding). Recovering animals are checked daily through the optimal edematous peak, which typically occurred by day 5-7. The plateau edematous peak are then observed. To evaluate the intensity of the lymphedema, the circumference and volumes of 2 designated places on each paw before operation and daily for 7 days are measured. The effect plasma proteins on lymphedema is determined and whether protein analysis is a useful testing perimeter is also investigated. The weights of both control and edematous limbs are evaluated at 2 places. Analysis is performed in a blind manner.

Circumference Measurements: Under brief gas anesthetic to prevent limb movement, a cloth tape is used to measure limb circumference. Measurements are done at the ankle bone and dorsal paw by 2 different people then those 2 readings are averaged. Readings are taken from both control and edematous limbs.

Volumetric Measurements: On the day of surgery, animals are anesthetized with Pentobarbital and are tested prior to surgery. For daily volumetrics animals are under brief halothane anesthetic (rapid immobilization and quick recovery), both legs are shaved and equally marked using waterproof marker on legs. Legs are first dipped in water, then dipped

into instrument to each marked level then measured by Buxco edema software(Chen/Victor). Data is recorded by one person, while the other is dipping the limb to marked area.

Blood-plasma protein measurements: Blood is drawn, spun, and serum separated prior to surgery and then at conclusion for total protein and Ca2+ comparison.

Limb Weight Comparison: After drawing blood, the animal is prepared for tissue collection. The limbs are amputated using a quillitine, then both experimental and control legs are cut at the ligature and weighed. A second weighing is done as the tibio-cacaneal joint is disarticulated and the foot is weighed.

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Histological Preparations: The transverse muscle located behind the knee (popliteal) area is dissected and arranged in a metal mold, filled with freezeGel, dipped into cold methylbutane, placed into labeled sample bags at - 80EC until sectioning. Upon sectioning, the muscle is observed under fluorescent microscopy for lymphatics..

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 30: Suppression of TNF alpha-induced adhesion molecule expression by a Agonist or Antagonist of the Invention

The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

Tumor necrosis factor alpha (TNF-a), a potent proinflammatory cytokine, is a stimulator of all three CAMs on endothelial cells and may be involved in a wide variety of inflammatory responses, often resulting in a pathological outcome.

The potential of an agonist or antagonist of the invention to mediate a suppression of TNF-a induced CAM expression can be examined. A modified ELISA assay which uses ECs as a solid phase absorbent is employed to measure the amount of CAM expression on TNF-a treated ECs when co-stimulated with a member of the FGF family of proteins.

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To perform the experiment, human umbilical vein endothelial cell (HUVEC) cultures are obtained from pooled cord harvests and maintained in growth medium (EGM-2; Clonetics, San Diego, CA) supplemented with 10% FCS and 1% penicillin/streptomycin in a 37 degree C humidified incubator containing 5% CO2. HUVECs are seeded in 96-well plates at concentrations of 1 x 10⁴ cells/well in EGM medium at 37 degree C for 18-24 hrs or until confluent. The monolayers are subsequently washed 3 times with a serum-free solution of RPMI-1640 supplemented with 100 U/ml penicillin and 100 mg/ml streptomycin, and treated with a given cytokine and/or growth factor(s) for 24 h at 37 degree C. Following incubation, the cells are then evaluated for CAM expression.

Human Umbilical Vein Endothelial cells (HUVECs) are grown in a standard 96 well plate to confluence. Growth medium is removed from the cells and replaced with 90 ul of 199 Medium (10% FBS). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 ul volumes). Plates are incubated at 37 degree C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 µl of 0.1% paraformaldehyde-PBS(with Ca++ and Mg++) is added to each well. Plates are held at 4°C for 30 min.

Fixative is then removed from the wells and wells are washed 1X with PBS(+Ca,Mg)+0.5% BSA and drained. Do not allow the wells to dry. Add 10 μl of diluted primary antibody to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 μg/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA.

Then add 20 μ l of diluted ExtrAvidin-Alkaline Phosphotase (1:5,000 dilution) to each well and incubated at 37°C for 30 min. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA. 1 tablet of p-Nitrophenol Phosphate pNPP is dissolved in 5 ml of glycine buffer (pH 10.4). 100 μ l of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphotase in glycine buffer: 1:5,000 (10°) > 10°0.5 > 10°1.5.5 μ l of each dilution is added to triplicate

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wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 µl of pNNP reagent must then be added to each of the standard wells. The plate must be incubated at 37°C for 4h. A volume of 50 µl of 3M NaOH is added to all wells. The results are quantified on a plate reader at 405 nm. The background subtraction option is used on blank wells filled with glycine buffer only. The template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 31: Production Of Polypeptide of the Invention For High-Throughput Screening Assays

The following protocol produces a supernatant containing polypeptide of the present invention to be tested. This supernatant can then be used in the Screening Assays described in Examples 33-42.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

Plate 293T cells (do not carry cells past P+20) at 2 x 10⁵ cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing

378

a polynucleotide insert, produced by the methods described in Examples 8-10, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

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Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37 degree C for 6 hours.

While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or HGS CHO-5 media (116.6 mg/L of CaCl2 (anhyd); 0.00130 mg/L CuSO₄-5H₂O; 0.050 mg/L of Fe(NO₃)₃-9H₂O; 0.417 mg/L of FeSO₄-7H₂O; 311.80 mg/L of Kcl; 28.64 mg/L of MgCl₂; 48.84 mg/L of MgSO₄; 6995.50 mg/L of NaCl; 2400.0 mg/L of NaHCO3; 62.50 mg/L of NaH2PO4-H20; 71.02 mg/L of Na2HPO4; .4320 mg/L of ZnSO4-7H₂O; .002 mg/L of Arachidonic Acid; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H20; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H₂0; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H₂0; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalainine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tryrosine-2Na-2H₂0; and 99.65 mg/ml of L-

Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; 0.680 mg/L of Vitamin B₁₂; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal Acetate. Adjust osmolarity to 327 mOsm) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37 degree C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 33-40.

It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide of the present invention directly (e.g., as a secreted protein) or by polypeptide of the present invention inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

Example 32: Construction of GAS Reporter Construct

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One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements

380

alter the expression of the associated gene.

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GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types. as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:838)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

381

•			<u>JAKs</u>			STATS GAS(elements) or ISRE		
	<u>Ligand</u>	tyk2	Jak I	Jak2	<u>Jak3</u>	STATE GAL	Section 15 to 15 t	
								
	IFN family							
5	IFN-a/B	+	+	•	•	1,2,3	ISRE	
	IFN-g		+	+	-	1	GAS (IRF1>Lys6>IFP)	
	II-10	+	?	?	-	1,3		
	gp130 family							
10	IL-6 (Pleiotrohic)	+	+	+	?	1,3	GAS (IRF1>Lys6>IFP)	
	Il-11(Pleiotrohic)	?	+	?	?	1,3		
	OnM(Pleiotrohic)	?	+	+	?	1,3		
	LIF(Pleiotrohic)	?	+	`+	?	1,3		
	CNTF(Pleiotrohic)	-/+	+	+	?	1,3		
15	G-CSF(Pleiotrohic)	?	+	?	?	1,3		
	IL-12(Pleiotrohic)	+ .	-	+	+	1,3		
	g-C family							
	IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS	
20	IL-4 (lymph/myeloid)	-	+	-	+	6	GAS (IRF1 = IFP	
	>>Ly6)(IgH)							
	IL-7 (lymphocytes)	-	+	-	+	5	GAS	
	IL-9 (lymphocytes)	-	+	-	+	5	GAS	
	IL-13 (lymphocyte)	-	+	?	?	6	GAS	
25	IL-15	?	+	?	+	5	GAS	
	gp140 family							
	IL-3 (myeloid)	••	-	+	-	5	GAS (IRF1>IFP>>Ly6)	
	IL-5 (myeloid)	-	-	+	-	5	GAS	
30	GM-CSF (myeloid)	-	. -	+	•	5	GAS	
	Growth hormone family	Ł						
	GH	?	-	+	-	5		
	PRL	?	+/-	+	-	1,3,5		
35	EPO	?	-	+	-	5	GAS(B-	

382

CAS>IRF1=IFP>>Ly6)

T.	_			
Receptor	1 1/1	OCIDA.	Kins	ACAC
receptor	1 y 1	OSILIO	121111	11303

	EGF	t	?	+	+	-	1,3	GAS (IRF1)
5	PDGF		?	+	+	-	1,3	
	CSF-1		?	+	+	-	1.3	GAS (not IRF1)

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 33-34, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

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5':GCGCCTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGATTTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:839)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:840)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':CTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAA TGATTTCCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCG CCCCTAACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCT CCGCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCC TCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTA
25 GGCTTTTGCAAAAAAGCTT:3' (SEQ ID NO:841)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol

acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using Sall and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 33-34.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 35 and 36. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, Il-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

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Example 33: High-Throughput Screening Assav for T-cell Activity.

The following protocol is used to assess T-cell activity by identifying factors, and determining whether supernate containing a polypeptide of the invention proliferates and/or differentiates T-cells. T-cell activity is assessed using the

GAS/SEAP/Neo construct produced in Example 32. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml genticin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

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Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

During the incubation period, count cell concentration, spin down the required number of cells (10⁷ per transfection), and resuspend in OPTI-MEM to a final concentration of 10⁷ cells/ml. Then add 1ml of 1 x 10⁷ cells in OPTI-MEM to T25 flask and incubate at 37 degree C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Genticin, and 1% Pen-Strep. These cells are treated with supernatants containing polypeptide of the present invention or polypeptide of the present invention induced polypeptides as produced by the protocol described in Example 31.

On the day of treatment with the supernatant, the cells should be washed and

resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).

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After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20 degree C until SEAP assays are performed according to Example 37. The plates containing the remaining treated cells are placed at 4 degree C and serve as a source of material for repeating the assay on a specific well if desired.

As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

The above protocol may be used in the generation of both transient, as well as, stable transfected cells, which would be apparent to those of skill in the art.

Example 34: High-Throughput Screening Assay Identifying Myeloid Activity

The following protocol is used to assess myeloid activity of polypeptide of the present invention by determining whether polypeptide of the present invention proliferates and/or differentiates myeloid cells. Myeloid cell activity is assessed using

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the GAS/SEAP/Neo construct produced in Example 32. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 32, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest 2x10e⁷ U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM Na₂HPO₄.7H₂O, 1 mM MgCl₂, and 675 uM CaCl₂. Incubate at 37 degrees C for 45 min.

Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37 degree C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

These cells are tested by harvesting $1x10^8$ cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of $5x10^5$ cells/ml. Plate 200 ul cells per well in the 96-well plate (or $1x10^5$ cells/well).

Add 50 ul of the supernatant prepared by the protocol described in Example 31. Incubate at 37 degee C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 37.

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When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed by polypeptide of the present invention.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells by polypeptide of the present invention can be assessed.

The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

- 5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:842)
 - 5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:843)

Using the GAS:SEAP/Neo vector produced in Example 32, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes Xhol/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and

allowed to air dry for 2 hr.

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PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heatinactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 31. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as $5x10^5$ cells/ml.

Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to 1×10^5 cells/well). Add 50 ul supernatant produced by Example 31, 37 degree C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 37.

Example 36: High-Throughput Screening Assay for T-cell Activity

NF-KB (Nuclear Factor KB) is a transcription factor activated by a wide

variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-KB regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- KB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF- KB is retained in the cytoplasm with I-KB (Inhibitor KB). However, upon stimulation, I- KB is phosphorylated and degraded, causing NF- KB to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- KB include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

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Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-KB promoter element are used to screen the supernatants produced in Example 31. Activators or inhibitors of NF-KB would be useful in treating, preventing, and/or diagnosing diseases. For example, inhibitors of NF-KB could be used to treat those diseases related to the acute or chronic activation of NF-KB, such as rheumatoid arthritis.

To construct a vector containing the NF-KB promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF-KB binding site (GGGGACTTTCCC) (SEQ ID NO:844), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGAC TTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:845)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:840)

PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with Xhol and Hind III and subcloned into BLSK2-. (Stratagene)

391

Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCC
ATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCC
ATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGA
CTAATTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTA
TTCCAGAAGTAGTGAGGAGGCTTTTTTTGGAGGCCTAGGCTTTTTGCAAAAA
GCTT:3' (SEO ID NO:846)

Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF-KB/SV40 fragment using Xhol and HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF-KB/SV40/SEAP cassette is removed from the above NF-KB/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF-KB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

Once NF-KB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 33. Similarly, the method for assaying supernatants with these stable Jurkat T-cells is also described in Example 33. As a positive control, exogenous TNF alpha (0.1,1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

Example 37: Assay for SEAP Activity

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As a reporter molecule for the assays described in Examples 33-36, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x

392

dilution buffer into Optiplates containing 35 ul of a supernatant. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 ml Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50 ul Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

Reaction Buffer Formulation:

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# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
H	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6
23	125	6.25

393

24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

Example 38: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

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For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO₂ incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37 degrees C in a CO₂ incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10⁶ cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37 degrees C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x10⁶ cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley Cell Wash with 200 ul, followed by an aspiration step to 100 ul final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as

395

fluo-4. The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event caused by the a molecule, either polypeptide of the present invention or a molecule induced by polypeptide of the present invention, which has resulted in an increase in the intracellular Ca⁺⁺ concentration.

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Example 40: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, identifying whether polypeptide of the present invention or a molecule induced by polypeptide of the present invention is capable of activating tyrosine kinase signal transduction pathways is of interest. Therefore, the following protocol

is designed to identify such molecules capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford,MA), or calf serum, rinsed with PBS and stored at 4 degree C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford,MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 31, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na3VO4, 2 mM Na4P2O7 and a cocktail of protease inhibitors (# 1836170) obtained from Boeheringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4

degree C at 16,000 x g.

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Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg₂₊ (5mM ATP/50mM MgCl₂), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl₂, 5 mM MnCl₂, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30 degree C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mm EDTA and place the reactions on ice.

Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degree C for 20 min. This allows the streptavadin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phospotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37 degree C for one hour. Wash the well as above.

Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of

398

tyrosine kinase activity.

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Example 41: High-Throughput Screening Assay Identifying Phosphorylation Activity

As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 40, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (lug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4 degree C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 31 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (lug/ml) which specifically recognizes the phosphorylated epitope of the

399

Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation by polypeptide of the present invention or a molecule induced by polypeptide of the present invention.

Example 42: Assay for the Stimulation of Bone Marrow CD34+ Cell Proliferation

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This assay is based on the ability of human CD34+ to proliferate in the presence of hematopoietic growth factors and evaluates the ability of isolated polypeptides expressed in mammalian cells to stimulate proliferation of CD34+ cells.

It has been previously shown that most mature precursors will respond to only a single signal. More immature precursors require at least two signals to respond. Therefore, to test the effect of polypeptides on hematopoietic activity of a wide range of progenitor cells, the assay contains a given polypeptide in the presence or absence of other hematopoietic growth factors. Isolated cells are cultured for 5 days in the presence of Stem Cell Factor (SCF) in combination with tested sample. SCF alone has a very limited effect on the proliferation of bone marrow (BM) cells, acting in such conditions only as a "survival" factor. However, combined with any factor exhibiting stimulatory effect on these cells (e.g., IL-3), SCF will cause a synergistic effect. Therefore, if the tested polypeptide has a stimulatory effect on a hematopoietic progenitors, such activity can be easily detected. Since normal BM cells have a low level of cycling cells, it is likely that any inhibitory effect of a given polypeptide, or agonists or antagonists thereof, might not be detected. Accordingly, assays for an inhibitory effect on progenitors is preferably tested in cells that are first subjected to in vitro stimulation with SCF+IL+3, and then contacted with the compound that is being evaluated for inhibition of such induced proliferation.

Briefly, CD34+ cells are isolated using methods known in the art. The cells are thawed and resuspended in medium (QBSF 60 serum-free medium with 1% L-

glutamine (500ml) Quality Biological. Inc., Gaithersburg, MD Cat# 160-204-101). After several gentle centrifugation steps at 200 x g, cells are allowed to rest for one hour. The cell count is adjusted to 2.5×10^5 cells/ml. During this time, $100 \mu l$ of sterile water is added to the peripheral wells of a 96-well plate. The cytokines that can be tested with a given polypeptide in this assay is rhSCF (R&D Systems, Minneapolis, MN, Cat# 255-SC) at 50 ng/ml alone and in combination with rhSCF and rhIL-3 (R&D Systems, Minneapolis, MN, Cat# 203-ML) at 30 ng/ml. After one hour, $10 \mu l$ of prepared cytokines, $50 \mu l$ of the supernatants prepared in Example 31 (supernatants at 1:2 dilution = $50 \mu l$) and $20 \mu l$ of diluted cells are added to the media which is already present in the wells to allow for a final total volume of $100 \mu l$. The plates are then placed in a 37° C/5% CO₂ incubator for five days.

Eighteen hours before the assay is harvested, 0.5 μCi/well of [3H] Thymidine is added in a 10 μl volume to each well to determine the proliferation rate. The experiment is terminated by harvesting the cells from each 96-well plate to a filtermat using the Tomtec Harvester 96. After harvesting, the filtermats are dried, trimmed and placed into OmniFilter assemblies consisting of one OmniFilter plate and one OmniFilter Tray. 60 μl Microscint is added to each well and the plate sealed with TopSeal-A press-on sealing film A bar code 15 sticker is affixed to the first plate for counting. The sealed plates is then loaded and the level of radioactivity determined via the Packard Top Count and the printed data collected for analysis. The level of radioactivity reflects the amount of cell proliferation.

The studies described in this example test the activity of a given polypeptide to stimulate bone marrow CD34+ cell proliferation. One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof. As a nonlimiting example, potential antagonists tested in this assay would be expected to inhibit cell proliferation in the presence of cytokines and/or to increase the inhibition of cell proliferation in the presence of cytokines and a given polypeptide. In contrast, potential agonists tested in this assay would be expected to enhance cell proliferation and/or to decrease the inhibition of cell proliferation in the presence of

401

cytokines and a given polypeptide.

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The ability of a gene to stimulate the proliferation of bone marrow CD34+ cells indicates that polynucleotides and polypeptides corresponding to the gene are useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein.

Example 43: Assav for Extracellular Matrix Enhanced Cell Response (EMECR)

The objective of the Extracellular Matrix Enhanced Cell Response (EMECR) assay is to identify gene products (e.g., isolated polypeptides) that act on the hematopoietic stem cells in the context of the extracellular matrix (ECM) induced signal.

Cells respond to the regulatory factors in the context of signal(s) received from the surrounding microenvironment. For example, fibroblasts, and endothelial and epithelial stem cells fail to replicate in the absence of signals from the ECM. Hematopoietic stem cells can undergo self-renewal in the bone marrow, but not in *in vitro* suspension culture. The ability of stem cells to undergo self-renewal *in vitro* is dependent upon their interaction with the stromal cells and the ECM protein fibronectin (fn). Adhesion of cells to fn is mediated by the α_5 . β_1 and α_4 . β_1 integrin receptors, which are expressed by human and mouse hematopoietic stem cells. The factor(s) which integrate with the ECM environment and responsible for stimulating stem cell self-renewal has not yet been identified. Discovery of such factors should be of great interest in gene therapy and bone marrow transplant applications

Briefly, polystyrene, non tissue culture treated, 96-well plates are coated with fn fragment at a coating concentration of $0.2~\mu g/~cm^2$. Mouse bone marrow cells are plated (1,000 cells/well) in 0.2~ml of serum-free medium. Cells cultured in the presence of IL-3 (5~ng/ml) + SCF (50~ng/ml) would serve as the positive control, conditions under which little self-renewal but pronounced differentiation of the stem

cells is to be expected. Gene products of the invention (e.g., including, but not limited to, polynucleotides and polypeptides of the present invention, and supernatants produced in Example 31), are tested with appropriate negative controls in the presence and absence of SCF(5.0 ng/ml), where test factor supernates represent 10% of the total assay volume. The plated cells are then allowed to grow by incubating in a low oxygen environment (5% CO₂, 7% O₂, and 88% N₂) tissue culture incubator for 7 days. The number of proliferating cells within the wells is then quantitated by measuring thymidine incorporation into cellular DNA. Verification of the positive hits in the assay will require phenotypic characterization of the cells, which can be accomplished by scaling up of the culture system and using appropriate antibody reagents against cell surface antigens and FACScan.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

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If a particular polypeptide of the present invention is found to be a stimulator of hematopoietic progenitors, polynucleotides and polypeptides corresponding to the gene encoding said polypeptide may be useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein. The gene product may also be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Additionally, the polynucleotides and/or polypeptides of the gene of interest and/or agonists and/or antagonists thereof, may also be employed to inhibit the proliferation and differentiation of hematopoietic cells and therefore may be employed to protect bone marrow stem cells from chemotherapeutic agents during chemotherapy. This antiproliferative effect may allow administration of higher doses of chemotherapeutic agents and, therefore, more effective chemotherapeutic treatment.

Moreover, polynucleotides and polypeptides corresponding to the gene of

interest may also be useful for the treatment and diagnosis of hematopoietic related disorders such as, for example, anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

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Example 44: Human Dermal Fibroblast and Aortic Smooth Muscle Cell Proliferation

The polypeptide of interest is added to cultures of normal human dermal fibroblasts (NHDF) and human aortic smooth muscle cells (AoSMC) and two coassays are performed with each sample. The first assay examines the effect of the polypeptide of interest on the proliferation of normal human dermal fibroblasts (NHDF) or aortic smooth muscle cells (AoSMC). Aberrant growth of fibroblasts or smooth muscle cells is a part of several pathological processes, including fibrosis, and restenosis. The second assay examines IL6 production by both NHDF and SMC. IL6 production is an indication of functional activation. Activated cells will have increased production of a number of cytokines and other factors, which can result in a proinflammatory or immunomodulatory outcome. Assays are run with and without co-TNFa stimulation, in order to check for costimulatory or inhibitory activity.

Briefly, on day 1, 96-well black plates are set up with 1000 cells/well (NHDF) or 2000 cells/well (AoSMC) in 100 μl culture media. NHDF culture media contains: Clonetics FB basal media, 1mg/ml hFGF, 5mg/ml insulin, 50mg/ml gentamycin, 2%FBS, while AoSMC culture media contains Clonetics SM basal media, 0.5 μg/ml hEGF, 5mg/ml insulin, 1μg/ml hFGF, 50mg/ml gentamycin, 50 μg/ml Amphotericin B, 5%FBS. After incubation at 37°C for at least 4-5 hours, culture media is aspirated and replaced with growth arrest media. Growth arrest media for NHDF contains fibroblast basal media, 50mg/ml gentamycin, 2% FBS, while growth arrest media for AoSMC contains SM basal media, 50mg/ml gentamycin, 50μg/ml Amphotericin B, 0.4% FBS. Incubate at 37°C until day 2.

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On day 2, serial dilutions and templates of the polypeptide of interest are designed such that they always include media controls and known-protein controls. For both stimulation and inhibition experiments, proteins are diluted in growth arrest media. For inhibition experiments, TNFa is added to a final concentration of 2ng/ml (NHDF) or 5ng/ml (AoSMC). Add 1/3 vol media containing controls or polypeptides of the present invention and incubate at 37°C/5% CO₂ until day 5.

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Transfer $60\mu l$ from each well to another labeled 96-well plate, cover with a plate-sealer, and store at $4^{\circ}C$ until Day 6 (for IL6 ELISA). To the remaining $100 \mu l$ in the cell culture plate, aseptically add Alamar Blue in an amount equal to 10% of the culture volume ($10\mu l$). Return plates to incubator for 3 to 4 hours. Then measure. fluorescence with excitation at 530nm and emission at 590nm using the CytoFluor. This yields the growth stimulation/inhibition data.

On day 5, the IL6 ELISA is performed by coating a 96 well plate with 50-100 ul/well of Anti-Human IL6 Monoclonal antibody diluted in PBS, pH 7.4, incubate ON at room temperature.

On day 6, empty the plates into the sink and blot on paper towels. Prepare Assay Buffer containing PBS with 4% BSA. Block the plates with 200 μ l/well of Pierce Super Block blocking buffer in PBS for 1-2 hr and then wash plates with wash buffer (PBS, 0.05% Tween-20). Blot plates on paper towels. Then add 50 μ l/well of diluted Anti-Human IL-6 Monoclonal, Biotin-labeled antibody at 0.50 mg/ml. Make dilutions of IL-6 stock in media (30, 10, 3, 1, 0.3, 0 ng/ml). Add duplicate samples to top row of plate. Cover the plates and incubate for 2 hours at RT on shaker. Plates are washed with wash buffer and blotted on paper towels. Dilute EU-labeled Streptavidin 1:1000 in Assay buffer, and add 100 μ l/well. Cover the plate and incubate 1 h at RT. Plates are again washed with wash buffer and blotted on paper towels. Add 100 μ l/well of Enhancement Solution and shake for 5 minutes. Read the plate on the Wallac DELFIA Fluorometer. Readings from triplicate samples in each assay are tabulated and averaged.

A positive result in this assay suggests AoSMC cell proliferation and that the polypeptide of the present invention may be involved in dermal fibroblast

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proliferation and/or smooth muscle cell proliferation. A positive result also suggests many potential uses of polypeptides, polynucleotides, agonists and/or antagonists of the polynucleotide/polypeptide of the present invention which gives a positive result. For example, inflammation and immune responses, wound healing, and angiogenesis, as detailed throughout this specification. Particularly, polypeptides of the present invention and polynucleotides of the present invention may be used in wound healing and dermal regeneration, as well as the promotion of vasculargenesis, both of the blood vessels and lymphatics. The growth of vessels can be used in the treatment of, for example, cardiovascular diseases. Additionally, antagonists of polypeptides and polynucleotides of the invention may be useful in treating diseases, disorders, and/or conditions which involve angiogenesis by acting as an anti-vascular (e.g., antiangiogenesis). These diseases, disorders, and/or conditions are known in the art and/or are described herein, such as, for example, malignancies, solid tumors, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; artheroscleric plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uvietis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis. Moreover, antagonists of polypeptides and polynucleotides of the invention may be useful in treating anti-hyperproliferative diseases and/or anti-inflammatory known in the art and/or described herein.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

Example 45: Cellular Adhesion Molecule (CAM) Expression on Endothelial Cells

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The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

Briefly, endothelial cells (e.g., Human Umbilical Vein Endothelial cells (HUVECs)) are grown in a standard 96 well plate to confluence, growth medium is removed from the cells and replaced with 100 μl of 199 Medium (10% fetal bovine serum (FBS)). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 μl volumes). Plates are then incubated at 37°C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 μl of 0.1% paraformaldehyde-PBS(with Ca++ and Mg++) is added to each well. Plates are held at 4°C for 30 min. Fixative is removed from the wells and wells are washed 1X with PBS(+Ca,Mg) + 0.5% BSA and drained. 10 μl of diluted primary antibody is added to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 μg/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed three times with PBS(+Ca,Mg) + 0.5% BSA. 20 μl of diluted ExtrAvidin-Alkaline Phosphotase (1:5,000 dilution, refered to herein as the working dilution) are added to

each well and incubated at 37°C for 30 min. Wells are washed three times with PBS(+Ca,Mg)+0.5% BSA. Dissolve I tablet of p-Nitrophenol Phosphate pNPP per 5 ml of glycine buffer (pH 10.4). 100 μ l of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphotase in glycine buffer: 1:5,000 (10°) > 10°.5 > 10

15 Example 46: Alamar Blue Endothelial Cells Proliferation Assay

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This assay may be used to quantitatively determine protein mediated inhibition of bFGF-induced proliferation of Bovine Lymphatic Endothelial Cells (LECs), Bovine Aortic Endothelial Cells (BAECs) or Human Microvascular Uterine Myometrial Cells (UTMECs). This assay incorporates a fluorometric growth indicator based on detection of metabolic activity. A standard Alamar Blue Proliferation Assay is prepared in EGM-2MV with 10 ng/ml of bFGF added as a source of endothelial cell stimulation. This assay may be used with a variety of endothelial cells with slight changes in growth medium and cell concentration. Dilutions of the protein batches to be tested are diluted as appropriate. Serum-free medium (GIBCO SFM) without bFGF is used as a non-stimulated control and Angiostatin or TSP-1 are included as a known inhibitory controls.

Briefly, LEC, BAECs or UTMECs are seeded in growth media at a density of 5000 to 2000 cells/well in a 96 well plate and placed at 37-C overnight. After the overnight incubation of the cells, the growth media is removed and replaced with

408

GIBCO EC-SFM. The cells are treated with the appropriate dilutions of the protein of interest or control protein sample(s) (prepared in SFM) in triplicate wells with additional bFGF to a concentration of 10 ng/ml. Once the cells have been treated with the samples, the plate(s) is/are placed back in the 37° C incubator for three days. After three days 10 ml of stock alamar blue (Biosource Cat# DAL1100) is added to each well and the plate(s) is/are placed back in the 37°C incubator for four hours. The plate(s) are then read at 530nm excitation and 590nm emission using the CytoFluor fluorescence reader. Direct output is recorded in relative fluorescence units.

Alamar blue is an oxidation-reduction indicator that both fluoresces and changes color in response to chemical reduction of growth medium resulting from cell growth. As cells grow in culture, innate metabolic activity results in a chemical reduction of the immediate surrounding environment. Reduction related to growth causes the indicator to change from oxidized (non-fluorescent blue) form to reduced (fluorescent red) form. i.e. stimulated proliferation will produce a stronger signal and inhibited proliferation will produce a weaker signal and the total signal is proportional to the total number of cells as well as their metabolic activity. The background level of activity is observed with the starvation medium alone. This is compared to the output observed from the positive control samples (bFGF in growth medium) and protein dilutions.

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Example 47: Detection of Inhibition of a Mixed Lymphocyte Reaction

This assay can be used to detect and evaluate inhibition of a Mixed Lymphocyte Reaction (MLR) by gene products (e.g., isolated polypeptides). Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by these polypeptides since the peripheral blood mononuclear fraction used in this assay includes T, B and

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natural killer lymphocytes, as well as monocytes and dendritic cells.

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Polypeptides of interest found to inhibit the MLR may find application in diseases associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus erythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma.

Briefly, PBMCs from human donors are purified by density gradient centrifugation using Lymphocyte Separation Medium (LSM[®], density 1.0770 g/ml, Organon Teknika Corporation, West Chester, PA). PBMCs from two donors are adjusted to 2 x 10⁶ cells/ml in RPMI-1640 (Life Technologies, Grand Island, NY) supplemented with 10% FCS and 2 mM glutamine. PBMCs from a third donor is adjusted to 2 x 10⁵ cells/ml. Fifty microliters of PBMCs from each donor is added to wells of a 96-well round bottom microtiter plate. Dilutions of test materials (50 μl) is added in triplicate to microtiter wells. Test samples (of the protein of interest) are added for final dilution of 1:4; rhuIL-2 (R&D Systems, Minneapolis, MN, catalog number 202-IL) is added to a final concentration of 1 μg/ml; anti-CD4 mAb (R&D Systems, clone 34930.11, catalog number MAB379) is added to a final concentration of 10 μg/ml. Cells are cultured for 7-8 days at 37°C in 5% CO₂, and 1 μC of [³H] thymidine is added to wells for the last 16 hrs of culture. Cells are harvested and thymidine incorporation determined using a Packard TopCount. Data is expressed as the mean and standard deviation of triplicate determinations.

Samples of the protein of interest are screened in separate experiments and compared to the negative control treatment, anti-CD4 mAb, which inhibits proliferation of lymphocytes and the positive control treatment, IL-2 (either as recombinant material or supernatant), which enhances proliferation of lymphocytes.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

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It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

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The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both incorporated herein by reference in their entireties. Moreover, the hard copy of and the corresponding computer readable form of the Sequence Listing of Serial No. 60/124,270 are also incorporated herein by reference in their entireties.

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Applicant's or agent's file reference number	PA103PCT	International application	, io.

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on page 72 , line	N/A
B. IDENTIFICATIONOF DEPOSIT	Further deposits are identified on an additional sheet
Name of depositary institution American Type Cultus	re Collection
Address of depositary institution (including postal code and cow 10801 University Bot	
Manassas, Virginia	20110-2209
United States of Ame	erica
	
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Address of depositary institution (including postal code and count 10801 University Bo Manassas, Virginia United States of Am	ulevard 20110-2209		
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10801 University Bo Manassas, Virginia United States of An	20110-2209
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The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

419

Page 2 ATCC Deposit No. 209061

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

	420		
Applicant's or agent's file reference number	PA103PCT	International application	

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A The indications made below relate to the microorganism referred to in the description on page 72 , line N/A B. IDENTIFICATIONOFDEPOSIT Further deposits are identified on an additional sheet American Type Culture Collection Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America Date of deposit 20 May 1997 209062 C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") The indications listed below with the international application This sheet was received by the International Bureau on:			
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ATCC Deposit No. 209062

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

422

Page 2 ATCC Deposit No. 209062

DENMARK

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SWEDEN

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NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

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Applicant's or agent's file reference number	PA103PCT	International application i	

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description	
on page, line	N/A .
B. IDENTIFICATIONOF DEPOSIT	Further deposits are identified on an additional sheet
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country)	
10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit	Accession Number
20 May 1997	209063
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	
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Authorized officer Volanda Harrod	Authorized officer
PCT/Internat'l Appl Processing Disc.	y Carlos
Form PCT/RO/134 (July 1992)	

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ATCC Deposit No. 209063

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection. the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

Page 2 ATCC Deposit No. 209063

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

Applicant's or agent's file	PA103PCT	International application	
reference number	PATUSPCT		

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

A. The indications made below relate to the microorganism reforming on page 72, line	erred to in the description N/A .
B. IDENTIFICATIONOFDEPOSIT	Further deposits are identified on an additional sheet
Name of depositary institution American Type Cult	ure Collection
Address of depositary institution (including postal code and co 10801 University B Manassas, Virginia United States of A	oulevard 20110-2209
Date of deposit	Accession Number
20 May 1997	209064
C. ADDITIONAL INDICATIONS (leave blank if not applic	able) This information is continued on an additional sheet
D. DESIGNATED STATES FOR WHICH INDICATI	ONS ARE MADE (if the indications are not for all designated States)
E. SEPARATE FURNISHING OF INDICATIONS (lea	
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ATCC Deposit No. 209064

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

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FINLAND

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UNITED KINGDOM

Page 2 ATCC Deposit No. 209064

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

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Applicant's or agent's file reference number	PA103PCT	International application	

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

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		10001 1	Iniversity Bou	levard
		Manaesa	is, Virginia	20110-2209
		United	States of Ame	erica
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Date of	- Tdeposit			Accession Number
		20 May 1997		209065
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ATCC Deposit No. 209065

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

Page 2 ATCC Deposit No. 209065

DENMARK

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SWEDEN

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NETHERLANDS

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Applicant's or agent's file	DATOSDOT	International application	
reference number	PA103PCT		
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description			
on page 72, line	N/A		
B. IDENTIFICATIONOF DEPOSIT	Further deposits are identified on an additional sheet		
Name of depositary institution			
American Type Culture	Collection		
Address of depositary institution (including postal code and country	(بر		
10801 University Boul Manassas, Virginia 2 United States of Amer	0110-2209		
Date of deposit	Accession Number		
20 May 1997	209066		
C. ADDITIONAL INDICATIONS (leave blank if not applicable	This information is continued on an additional sheet		
D. DESIGNATED STATES FOR WHICH INDICATION	IS ARE MADE (if the indications are not for all designated States)		
E. SEPARATE FURNISHING OF INDICATIONS (leave b.			
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")			
For receiving Office use only	For International Bureau use only		
This sheet was received with the international application	This sheet was received by the International Bureau on:		
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Authorized offices in Ligand	Authorized officer		
Authorized officering Herrod Perfensement'i Appl Processing DNL			
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Form PCT/RO/134 (July 1992)

433

ATCC Deposit No. 209066

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

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UNITED KINGDOM

434

Page 2 ATCC Deposit No. 209066

DENMARK

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NETHERLANDS

	435		
Applicant's or agent's file reference number	PA103PCT	International application	

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

A. The indications made below relate to the microorganism referred to in the description on page			
B. IDENTIFICATIONOFDE	POSIT	Further deposits are identified on an additional sheet	
Name of depositary institution	American Type Cultur	re Collection	
Address of depositary institutio	n (including postal code and count	(יִי)	
	10801 University Boo Manassas, Virginia United States of Ame	20110-2209	
Date of deposit		Accession Number	
20 Ma	y 1997	209067	
C. ADDITIONAL INDICAT	FIONS (leave blank if not applicabl	e) This information is continued on an additional sheet	
D. DESIGNATED STATES	FOR WHICH INDICATION	NS ARE MADE (if the indications are not for all designated States)	
	- CONTROL TIONS	1.17 P. H.)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")			
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	the international application	For International Bureau use only This sheet was received by the International Bureau on: Authorized officer	
Form PCT/RO/134 (July 1992)	,		

436

ATCC Deposit No. 209067

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

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UNITED KINGDOM

437

Page 2 ATCC Deposit No. 209067

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NETHERLANDS

Applicant's or agent's file reference number	PA103PCT	International application -

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A. The indications made below relate to the microorganism referred to in the description on page			
B. IDENTIFICATIONOF DEPOSIT	Further deposits are identified on an additional sheet		
Name of depositary institution American Type Cultur	re Collection		
Address of depositary institution (including postal code and count	ייי)		
10801 University Boo Manassas, Virginia United States of Ame	20110-2209		
Date of deposit	Accession Number		
20 May 1997	209068		
C. ADDITIONAL INDICATIONS (leave blank if not applicable	This information is continued on an additional sheet		
D. DESIGNATED STATES FOR WHICH INDICATION	NS ARE MADE (if the indications are not for all designated States)		
E. SEPARATE FURNISHING OF INDICATIONS (leave t	blank if not applicable)		
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")			
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439

ATCC Deposit No. 209068

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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UNITED KINGDOM

Page 2 ATCC Deposit No. 209068

DENMARK

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NETHERLANDS

Applicant's or agent's file reference number

441		
	International application	

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

PA103PCT

A. The indication	ons made below relate to the	e microorganism ref	erred to in the description
on page	72	line	N/A
B. IDENTIFIC	CATIONOFDEPOSIT		Further deposits are identified on an additional sheet
Name of deposit			
	America	an Type Cultu	ure Collection
Address of depo	ositary institution (includin	g postal code and co	untry)
	10801 U	Jniversity Bo	pulevard
		s, Virginia	
	United	States of Ar	nerica
Date of deposit			Accession Number
	20 May 1997		209069
C. ADDITIO	NAL INDICATIONS (le	ave blank if not applic	able) This information is continued on an additional sheet
D. DESIGNA	TED STATES FOR WH	HICH INDICATION	ONS ARE MADE (if the indications are not for all designated States)
E SEDADAT	E FURNISHING OF IN	DICATIONS(lea	ve blank if not applicable)
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")			
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Thip Cy		ational application	This sheet was received by the International Bureau on:
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Form PCT/RO/134 (July 1992)

ATCC Deposit No. 209069

CANADA

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NORWAY

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UNITED KINGDOM

443

Page 2 ATCC Deposit No. 209069

DENMARK

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Form PCT/RO/134 (July 1992)

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Applicant's or agent's file reference number	PA103PCT	International application			
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

A. The indications made below relate to the microorganism refer	
onpage 72 , line	N/A .
B. IDENTIFICATIONOF DEPOSIT	Further deposits are identified on an additional sheet
Name of depositary institution American Type Cultur	re Collection
Address of depositary institution (including postal code and coun.	(יְיוֹי
10801 University Bou Manassas, Virginia United States of Ame	20110-2209
Date of deposit	Accession Number
12 January 1998	209579
C. ADDITIONAL INDICATIONS (leave blank if not applicable	(le) This information is continued on an additional sheet
D. DESIGNATED STATES FOR WHICH INDICATION	NS ARE MADE (if the indications are not for all designated States)
E. SEPARATE FURNISHING OF INDICATIONS (leave	blank if not applicable)
	nal Bureau later (specify the general nature of the indications e.g., "Accession
For receiving Office use only	For International Bureau use only
This sheet was received with the international application	This sheet was received by the International Bureau on:
Authorized officer	Authorized officer
College Service Services	<u>.</u>

ATCC Deposit No. 209579

CANADA

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UNITED KINGDOM

Page 2 ATCC Deposit No. 209579

DENMARK

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NETHERLANDS

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Applicant's or agent's file reference number	PA103PCT	International application

PCT/US00/05881

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

A. The indications made below relate to the microorganism referred on page 72 line	ed to in the description N/A .
B. IDENTIFICATIONOF DEPOSIT	Further deposits are identified on an additional sheet
Name of depositary institution American Type Cultur	e Collection
Address of depositary institution (including postal code and country	yJ
10801 University Bou Manassas, Virginia United States of Ame	20110-2209
Date of deposit 12 January 1998	Accession Number 209578
C. ADDITIONAL INDICATIONS (leave blank if not applicable	This information is continued on an additional sheet
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D. DESIGNATED STATES FOR WHICH INDICATION	NS ARE MADE (if the indications are not for all designated States)
E. SEPARATE FURNISHING OF INDICATIONS (leave be	plank if not applicable)
The indications listed below will be submitted to the Internation Number of Deposit")	nal Bureau later (specify the general nature of the indications e.g., "Accession
For receiving Office use only	For International Bureau use only
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Authorized officer Yolsında Harrod PCT/Internat'i Appi Processing Div.	Authorized officer
Form PCT/RO/134 (July 1992)	1 <u> </u>

ATCC Deposit No. 209578

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

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UNITED KINGDOM

Page 2 ATCC Deposit No. 209578

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NETHERLANDS

Form PCT/RO/134 (July 1992)

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Applicant's or agent's file reference number	PA103PCT	International application

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

A. The indications made below relate to the microorganism referred to in the description on page			
B. IDENTIFICATIONOF DEPOSIT	Further deposits are identified on an additional sheet		
Name of depositary institution			
American Type Cultu	re Collection		
Address of depositary institution (including postal code and count	ry)		
10801 University Boulevard Manassas, Virginia 20110-2209 United States of America			
	N. N.		
Date of deposit 16 July 1998	Accession Number 203067		
C. ADDITIONAL INDICATIONS (leave blank if not applicable	e) This information is continued on an additional sheet		
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)			
E. SEPARATE FURNISHING OF INDICATIONS (leave b	olank if not applicable)		
	nal Bureau later (specify the general nature of the indications e.g., "Accession		
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For receiving Office use only	For International Bureau use only		
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RO/US 03 MAR 2000			
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ATCC Deposit No. 203067

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

Page 2 ATCC Deposit No. 203067

DENMARK

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SWEDEN

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NETHERLANDS

		453
Applicant's or agent's file reference number	PA103PCT	International application

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

A. The indications made below relate to the microorganism refe	rred to in the description
on page	N/A
B. IDENTIFICATIONOF DEPOSIT	Further deposits are identified on an additional sheet
Name of depositary institution	
American Type Cult	ure Collection
Address of depositary institution (including postal code and cour	wy
10801 University B	
Manassas, Virginia	
United States of A	merica
Date of deposit	Accession Number
16 July 1998	203068
C. ADDITIONAL INDICATIONS (leave blank if not applical	ole) This information is continued on an additional sheet
D. DESIGNATED STATES FOR WHICH INDICATIO	NS ARE MADE (if the indications are not for all designated states)
E. SEPARATE FURNISHING OF INDICATIONS (leave	
The indications listed below will be submitted to the internation Number of Deposit")	onal Bureau later (specify the general nature of the indications e.g., "Accession
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RO/US 0.8 MAR 2000	Authorized officer
Yolanda Harrod	
PCT/Internat ⁴ l Appl Processing Div.	<u> </u>
orm PCT/RO7/34 Hilly 1992)	

454

ATCC Deposit No. 203068

CANADA

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UNITED KINGDOM

Page 2 ATCC Deposit No. 203068

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NETHERLANDS

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Applicant's or agent's file reference number	PA103PCT	International application?

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

	v relate to the microorganism refer 2, line	red to in the description N/A .
B. IDENTIFICATIONOFD	EPOSIT	Further deposits are identified on an additional sheet
Name of depositary institution		
	American Type Cultur	re Collection
Address of depositary institut	ion (including postal code and coun	וְיַנְיִי
	10801 University Bou Manassas, Virginia United States of Ame	20110-2209
Date of deposit		Accession Number
1 Febr	uary 1999	203609
C. ADDITIONAL INDICA	TIONS (leave blank if not applicab	(e) This information is continued on an additional sheet
D. DESIGNATED STATE	S FOR WHICH INDICATIO	NS ARE MADE (if the indications are not for all designated States)
	ING OF INDICATIONS (leave	
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,	Office use only	For International Bureau use only
RO/US US	MARZOOO application	This sheet was received by the International Bureau on:
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PCT/Internat'i A	Appl Processing Div.	
703) 305 067 orm PCT/RO/134 (July 1992)	·.	

457

ATCC Deposit No. 203609

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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UNITED KINGDOM

458

Page 2 ATCC Deposit No. 203609

DENMARK

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NETHERLANDS

		459	
Applicant's or agent's file reference number	PA103PCT	International application 1	

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

A. The indications made below relate to the microorganism referred to in the description on page	
B. IDENTIFICATIONOFDEPOSIT	Further deposits are identified on an additional sheet
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country)	
10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit	Accession Number
1 February 1999	203610
C. ADDITIONAL INDICATIONS (leave blank if not applicable	This information is continued on an additional sheet
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	
For receiving Office use only	For International Bureau use only
This sheet was received with the international application RO/US 0 0 MAR 2000	This sheet was received by the International Bureau on:
Authorized offic Yelanda Harrod PCT/Internat'l Appl Processing Div. (703) 305-3670	Authorized officer

460

ATCC Deposit No. 203610

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

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UNITED KINGDOM

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Page 2 ATCC Deposit No. 203610

DENMARK

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NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

	462	
Applicant's or agent's file reference number	PA103PCT	International application f

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism refe	rred to in the description	
on page, line	N/A .	
B. IDENTIFICATIONOF DEPOSIT	Further deposits are identified on an additional sheet	
Name of depositary institution		
American Type Cultu	ure Collection	
Address of depositary institution (including postal code and could	nıry)	
10801 University Bo		
Manassas, Virginia		
United States of An	nerica	
Date of deposit	Accession Number	
17 November 1998	203485	
C. ADDITIONAL INDICATIONS (leave blank if not application)	ble) This information is continued on an additional sheet	
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D. DESIGNATED STATES FOR WHICH INDICATION	ONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave	e blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")		
Namber of Deposit y		
For receiving Office use only	For International Bureau use only	
This sheet was received with the international application	This sheet was received by the International Bureau on:	
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Form PCT/RO/134 (July 1992)

ATCC Deposit No. 203485

CANADA

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NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

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Page 2 ATCC Deposit No. 203485

DENMARK

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SWEDEN

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NETHERLANDS

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Applicant's or agent's file reference number	PA103PCT	International application f

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page		
B. IDENTIFICATIONOF DEPOSIT	Further deposits are identified on an additional sheet	
Name of depositary institution American Type Cultu	re Collection	
American Type Culture Collection		
Address of depositary institution (including postal code and count	(n)	
10801 University Boulevard Manassas, Virginia 20110-2209 United States of America		
Date of deposit	Accession Number	
18 June 1999	PTA-252	
C. ADDITIONAL INDICATIONS (leave blank if not applicable	This information is continued on an additional sheet	
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D. DESIGNATED STATES FOR WHICH INDICATION	NS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave		
The indications listed below will be submitted to the Internation Number of Deposit")	nal Bureau later (specify the general nature of the indications e.g., "Accession	
For receiving Office use only	For International Bureau use only	
This sheet was received with the international application RO/US 08 MAR 2000	This sheet was received by the International Bureau on:	
Authorized officer	Authorized officer	
Yolanda Harrod PCT/Internat'l Appl Processing Dist.	197	
Form PCT/RO/134 (Ail) 1992)-36 /13		

ATCC Deposit No. PTA-252

CANADA

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UNITED KINGDOM

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467

Page 2 ATCC Deposit No. PTA-252

DENMARK

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Applicant's or agent's file reference number	PA103PCT	International application N°	

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page			
B. IDENTIFICATIONOF DEPOSIT	Further deposits are identified on an additional sheet		
Name of depositary institution			
American Type Cultu	re Collection		
Address of depositary institution (including postal code and coun	try)		
10801 University Bot			
Manassas, Virginia United States of Am			
Date of deposit	Accession Number		
18 June 1999	PTA-253		
C. ADDITIONAL INDICATIONS (leave blank if not applicab	le) This information is continued on an additional sheet		
D. DESIGNATED STATES FOR WHICH INDICATIO	NS ARE MADE (if the indications are not for all designated States)		
TO THE PROPERTY OF THE PROPERT	Harristan and Harristan		
E. SEPARATE FURNISHING OF INDICATIONS (leave			
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")			
For receiving Office use only	For International Bureau use only		
This sheet was received with the international application	This sheet was received by the International Bureau on:		
Authorized of Yols, nda Harrod	Authorized officer		
PCT/Internat'l Appl Processing Div.			
(703) 305-3670	7		

Form PCT/RO/134 (July 1992)

ATCC Deposit No. PTA-253

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

470

Page 2 ATCC Deposit No. PTA-253

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

	471		
Applicant's or agent's file reference number	PA103PCT	International application ?	

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page			
B. IDENTIFICATIONOFDEPOSIT	Further deposits are identified on an additional sheet		
Name of depositary institution			
American Type Cultu	re Collection		
Address of depositary institution (including postal code and coun	iry)		
10801 University Boulevard Manassas, Virginia 20110-2209 United States of America			
Date of deposit	Accession Number		
22 December 1999	PTA-1081		
C. ADDITIONAL INDICATIONS (leave blank if not applicab	le) This information is continued on an additional sheet		
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)			
E. SEPARATE FURNISHING OF INDICATIONS (leave			
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")			
For receiving Office use only	For International Bureau use only		
This sheet was received with the international application RO/US 03 MAR 2000	This sheet was received by the International Bureau on:		
Authorized Alanda Harrod	Authorized officer		
PCT/Internat'i Appi Processing Div. (703) 305-3670			

ATCC Deposit No. PTA-1081

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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FINLAND

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UNITED KINGDOM

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Page 2 ATCC Deposit No. PTA-1081

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

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What Is Claimed Is:

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- 1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:
- (a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
- (b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
 - (c) a polynucleotide encoding a polypeptide fragment of a polypeptide encoded by SEQ ID NO:X or a polypeptide fragment encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
 - (d) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
 - (e) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
 - (f) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X, having biological activity;
 - (g) a polynucleotide which is a variant of SEQ ID NO:X;
 - (h) a polynucleotide which is an allelic variant of SEQ ID NO:X;
 - (i) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;
- (j) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide

PCT/US00/05881

sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a protein.

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3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X.

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4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X.

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5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

- 6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.
- 7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.
 - 8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.
- 30 9. A recombinant host cell produced by the method of claim 8.

- 10. The recombinant host cell of claim 9 comprising vector sequences.
- 11. An isolated polypeptide comprising an amino acid sequence at least 5 95% identical to a sequence selected from the group consisting of:
 - (a) a polypeptide fragment of SEQ ID NO:Y or of the sequence encoded by the cDNA included in the related cDNA clone;
 - (b) a polypeptide fragment of SEQ ID NO:Y or of the sequence encoded by the cDNA included in the related cDNA clone, having biological activity;
- (c) a polypeptide domain of SEQ ID NO:Y or of the sequence encoded by the cDNA included in the related cDNA clone;
 - (d) a polypeptide epitope of SEQ ID NO:Y or of the sequence encoded by the cDNA included in the related cDNA clone;
- (e) a full length protein of SEQ ID NO:Y or of the sequence encoded by the cDNA included in the related cDNA clone;
 - (f) a variant of SEQ ID NO:Y;
 - (g) an allelic variant of SEQ ID NO:Y; or
 - (h) a species homologue of the SEQ ID NO:Y.
- 20 12. The isolated polypeptide of claim 11, wherein the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.
- 13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.
 - 14. A recombinant host cell that expresses the isolated polypeptide of claim 11.
- 30 15. A method of making an isolated polypeptide comprising:

477

- (a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and
 - (b) recovering said polypeptide.
- 5 16. The polypeptide produced by claim 15.
 - 17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

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- 18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:
- (a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and
- (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.
 - 19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:
 - (a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and
 - (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.
 - 20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:
 - (a) contacting the polypeptide of claim 11 with a binding partner; and
 - (b) determining whether the binding partner effects an activity of the polypeptide.

- 21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.
- 22. A method of identifying an activity in a biological assay, wherein the method comprises:
- 5 (a) expressing SEQ ID NO:X in a cell;
 - (b) isolating the supernatant;
 - (c) detecting an activity in a biological assay; and
 - (d) identifying the protein in the supernatant having the activity.
- The product produced by the method of claim 20.

PCT/US00/05881

WO 00/55173

1

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PCT/US00/05881

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WO 00/55173

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tggaggttcc caggaggcat gttcttgatg cctgtgntgc ctgaatccaa ttaactgaat 180
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cctqctqata ccqattcccc tqacatttca qqctaaaqcc aqcaqqraaq qqctaqqqac 540
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<211> 624
<212> DNA
<213> Homo sapiens
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accagttaaa gaatttagaa tatattagat cccatctagt attatatatt ttttctagtt 240
gatcattgag cagtaaatac caaatactcg attagaaggt aatttttaca ttgttttgaa 300
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aarggaatgt ctgttgatat tctgagtcga ttttcatttg cttttgttcc agaacggtta 600
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<211> 301
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<213> Homo sapiens
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<221> misc feature
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cagtocotga toogacaggo cagagtgtoa atgogococo tgotatocag coattggatg 180
acgaggatgt atttctctgc gggaagtgta agaagcaatt caactcgctg ccagcgttta 240
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С
<210> 9
<211> 686
<212> DNA
<213> Homo sapiens
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cagctgttca tccatttcgt gttttttcct gtcaaacatt aatccagcaa atatatgagg 180
tátttaccaa tttattttct tagtattaca aaataattca ttagcataaa gtacaatagt 240
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tctctcttgt aagtgttaaa tgtgataaaa gtacatattt taaattgttt tcagctcttg 600
gatatagcag caataaaaac actaatttgt gggtatttaa gaaaacctgg agaataaact 660
catactttaa aagatcaaaa aaaaaa
<210> 10
<211> 397
<212> DNA
<213> Homo sapiens
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<221> misc feature
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<223> n equals a,t,g, or c
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<221> misc feature
<222> (394)
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PCT/US00/05881

WO 00/55173

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cygggcgagg agcgcctcta caaccccttc ctgcgggtgg cgtgagtatg gctgttgtcc 180
eggggeetee acceptacet ggaccettag gaaggeatet ggggactgeg tgttgggetg 240
agtgagcatc tetggettgg gggaggetge teattaagtg cetgeetgee egsecamece 300
toggogocat gotocogogt gggcagoggg cootgogoot cactgcacco otocotgcag 360
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<211> 563
<212> DNA
<213> Homo sapiens
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tatattgcta ctcattcaag aatcctcaat aagtattgag tatttaccat atgttgggat 420
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aaaatgkgta atatttattc ccccattaan taactggact agggaaggga ctaaaaaggcc 540
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agaaaggggg atgaaaaaaa ant
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PCT/US00/05881

WO 00/55173

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<211> 443
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<213> Homo sapiens
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<212> DNA
<213> Homo sapiens
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<221> misc feature
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<222> (681)
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<222> (713)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (2413)
<223> n equals a,t,g, or c
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PCT/US00/05881 WO 00/55173

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13

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PCT/US00/05881

WO 00/55173 PCT/

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<222> (2003)
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<222> (2007)
<223> n equals a,t,g, or c
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<222> (358)

<211> 411

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<211> 657
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<213> Homo sapiens
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<213> Homo sapiens
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<213> Homo sapiens
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<211> 1327
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<213> Homo sapiens
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<222> (573)
<223> n equals a,t,g, or c
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<222> (1325)
<223> n equals a,t,g, or c
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<211> 709
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<213> Homo sapiens
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<221> misc feature
<222> (696)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (701)
<223> n equals a,t,g, or c
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<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (397)
<223> n equals a,t,g, or c
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PCT/US00/05881

WO 00/55173

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<223> n equals a,t,g, or c
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<222> (335)
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<221> misc feature
<222> (1413)
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<222> (1526)
<223> n equals a,t,g, or c
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caatgcgatg tatattaaac tttttataaa agttaacatt ttgcataata aacgattttt 1260
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30

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cacgggggtg gttgtcctgg ccggcgccct gctggaagga ggccgagcag ctgctggacc 360
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gagca
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<213> Homo sapiens
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<221> misc feature
<222> (33)
<223> n equals a,t,g, or c
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<223> n equals a,t,g, or c
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WO 00/55173

32

<220>

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<222> (1149)
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<222> (1156)
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<222> (1160)
<223> n equals a,t,g, or c
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tttgtggatc gctgtgatcg tcacttgaca atgcagatct tcgtgaagac tctgactggt 120
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<221> misc feature
<222> (217)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (465)
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<223> n equals a,t,g, or c
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geggetggae geegaeeeet eeeteeageg ggtgegeeag gaggagageg ageagateaa 180
gacceteaac aacaagtttg ceteetteat egacaaggtg eggtttetgg agcageagaa 240
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<222> (1629)
<223> n equals a,t,g, or c
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geggeetggg tgeeggetee tgeaggetgg gatetgetgg eggeetggge ageaeeteg 240
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aqtactacaq gacaattgag gagctgcaga acaagatcct cacagccacc gtggacaatg 540
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aagaggteca ggatggeaag gteateteet eeegegagea ggteeaceag accaeeeget 1380
gaggactcag ctaccccggc cggccacca ggaggcaggg angcagccgc cccatctgcc 1440
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<210> 52
<211> 1780
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> (1780)
<223> n equals a,t,g, or c
<400> 52
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taatgcctct gtctagcatg ccaacaagaa tgcattgata ttgtgaacat ttgtgatata 1740
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<210> 53
<211> 490
<212> DNA
<213> Homo sapiens
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PCT/US00/05881

WO 00/55173

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caaaattgag tgcttgattt taggttttat ttttttatga atgtccaaat ctgtgtttcc 300
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490
aaaaaaaaa
<210> 54
<211> 1944
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (466)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (634)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (1308)
<223> n equals a,t,g, or c
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<211> 994
<212> DNA
<213> Homo sapiens
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<223> n equals a,t,g, or c
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<222> (971)
<223> n equals a,t,g, or c
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<210> 56
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<211> 328

PCT/US00/05881 WO 00/55173

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<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (123)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (156)
<223> n equals a,t,g, or c
<220>
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<222> (170)
<223> n equals a,t,g, or c
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tanggegegg tggetcacge etgtaateee cacaenttgg gaaggeegan geaggeggat 180
cacgaggtca gaagattgag accattctgg ctaacatggt gaacccccat ctctactaaa 240
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<210> 57
<211> 1489
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (710)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (1109)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (1117)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (1206)
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PCT/US00/05881

WQ 00/55173

<220>

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<221> misc feature
<222> (1211)
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<221> misc feature
<222> (1264)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (1311)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (1446)
<223> n equals a,t,q, or c
<220>
<221> misc feature
<222> (1467)
<223> n equals a,t,g, or c
<400> 57
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<212> DNA
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<221> misc feature
<222> (1263)
<223> n equals a,t,g, or c
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<211> 740
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (696)
<223> n equals a,t,g, or c
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<211> 1291
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> (6)
<223> n equals a,t,g, or c
<220>
<221> misc feature
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WO 00/55173

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<222> (7)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (147)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (1211)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (1283)
<223> n equals a,t,g, or c
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WO 00/55173

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PCT/US00/05881 WO 00/55173

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PCT/US00/05881

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WO 00/55173

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<222> (1424)

WO 00/55173

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PCT/US00/05881 WO 00/55173

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PCT/US00/05881

WO 00/55173 P

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<222> (2497)
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<400> 88
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<223> n equals a,t,g, or c
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catcgatgag gctggccact gcatggagcc tgagaagtct ggtagctata gcagggctga 180
tggaagtaaa ggaaacaggt gatccaggag ggcagctggt gctggcagga gaccctcggc 240
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accageteta ttatgaaggg gagetgeagg cetgtgetga tgtegtggat egagaaeget 480
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PCT/US00/05881

70

WO 00/55173

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<212> DNA
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<222> (1333)
<223> n equals a,t,g, or c
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aaaagggggg ccgcccaagg grtncccccg aggggggccc cagctttacg cgtggcntgc 1320
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PCT/US00/05881

WO 00/55173

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<211> 787
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<222> (677)
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<222> (742)
<223> n equals a,t,g, or c
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<213> Homo sapiens
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WO 00/55173

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ctacagtgaa gatteteatt acaacagtge cacceaatet tegaaaaetg gateeagaae 660
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<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> (478)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (485)
<223> n equals a,t,g, or c
<400> 93
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                                                                  485
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<210> 94
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<212> DNA
<213> Homo sapiens
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WO 00/55173 PCT

73

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<222> (202)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (565)
<223> n equals a,t,g, or c
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<210> 95
<211> 707
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> (45)
<223> n equals a,t,g, or c
<400> 95
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<210> 96

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<211> 815
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> (45)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (50)
<223> n equals a,t,g, or c
<400> 96
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caagcccgaa gatgccccc attctctwag tgatggcggc gttagggttt gagagaaggg 180
aatttggctc aacttcagtt gagagggtgc agtccagaca gcttgactgc ttttaaatga 240
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gaattaattt gaatgttttt tacactaact aacttttccc aataaagtcc actatgaaac 780
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<211> 658
<212> DNA
<213> Homo sapiens
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<222> (634)
<223> n equals a,t,g, or c
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<222> (635)
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<211> 249
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
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<223> n equals a,t,g, or c
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249
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<210> 99
<211> 752
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (612)
<223> n equals a,t,g, or c
<400> 99
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tgcgggcgcc ccctctgcgg ggtcctggcc acgtgctcct gcgctacgac agcgccgtgg 240
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WO 00/55173

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<211> 711
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<213> Homo sapiens
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<222> (642)
<223> n equals a,t,g, or c
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gattagaata tgtatccaaa tggcattcac gtgtcactta gcaaggtttg ctgatgcttc 240
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aacgggatga ggtgttacag ctgcctccct cttcatgcaa tctggtgagc agtggtgcag 360
gcggggagcc agagaaactt gccagttata taacttctct ttggcttttc ttcatctgta 420
aaacaaggat aatactgaac tgtaagggtt agtggagagt ttttaattaa aagaatgtgt 480
gaaaagtaca tgacacagta gttgcttgat aatagttact agtagtagta ttcttactaa 540
gacccaatac aaatggatta tttaaaccaa gtttatgagt tggtttttt cattttcyat 600
ttgtatttta ttaagagtgc ttttcttatg gtgattttt tnaattgcga tttgatatgg 660
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tttggccata tggccccacc caaatcccca tcttggatta taatccccat g
<210> 109
<211> 743
<212> DNA
<213> Homo sapiens
<400> 109
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atttcatatt atataattct gcttattctt tcaaaaattt atacatccat tgggcaagga 180
atggttttca ttaaattacc aatattaaat gcacttaatc attgtgtata ggttaaacca 240
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aatatttgat gcaaatatgc agataaaatt ttttaaaaaat tagaacactg agtaaaacac 360
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aaaacactca gctttggttt ctttgtttcc caaactgcaa agctgctgat aacaaaactc 480
caggattcca tgtgagttca gctatgtcta ctttaacaca aatattaaaa cagaattcag 540
raaatgcagt attaaggatc cagcttctat tgaaaccaat atccatttgc atcataacaa 600
caaacatttg aatgagatgg tcacacttgt acttatcagc aggttccttt aataacaaag 660
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actactaaat gtatatcctt aatcacaaaa gaacaacaaa aaaaatacag gttttttttt 720
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<210> 110
<211> 795
<212> DNA
<213> Homo sapiens
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<221> misc feature
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<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (645)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (737)
<223> n equals a,t,g, or c
<400> 110
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atattatatg tggtttataa gctcaacact ggccattttt ttagttttat tgttaaatgg 180
tatttttcta tgtttaatta taatagatct ggctttttct ggatagcata aagatcactg 240
aactatatat atataagara caagagttct attttagcac aaaggcattt tatattattt 300
attgaatcca taagtttgtt ttcgtcaaaa acattccata ttatttctgc tcctttttat 360
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caagtaccgc aaaggcttta ttctggactg gctatctcat aaaanggatt tctgtaagac 660
tttgcagtgt cattccctca gaaccyaggt ttgtttctaa agccacggta ttgtccrrgr 720
recectgtgt ktggggneag gtagetatee eteceatgte attagtaate etttaggatt 780
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<210> 111
<211> 1332
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> (1)
<223> n equals a,t,g, or c
<220>
<221> misc feature
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WO 00/55173

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<222> (6)
<223> n equals a,t,q, or c
<220>
<221> misc feature
<222> (1194)
<223> n equals a,t,g, or c
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<222> (1237)
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<220>
<221> misc feature
<222> (1241)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (1300)
<223> n equals a,t,g, or c
<400> 111
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ceteagacce tecceacate tgaaactgee tecceecaac caccageage ageagggeec 180
tectececca ceagetetee ceaeagggee ceteageate atggagaeec geagegggge 240
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agagececae ttteetaact egtgeteeet teegeettet ttteegtaet gtgaagaaag 360
aactetecae eccagetece accetgeeet ggeetgggtg gaggaactgt geetecatee 420
ccagaagaaa cagcccctc tgctgctggg gtgggactgt ctgtgtgccc tgtgggggtc 480
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gaccccggct yeacacccac atccagcctg caggcctctc tgcagtcctc tcaccctccc 780
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acggggagcc ctttcttccc tggaccctgg ggcttgnttc ntgggggggc tcttccaaga 1260
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aaggcaaaag ag
<210> 112
<211> 743
<212> DNA
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PCT/US00/05881 WO 00/55173

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<213> Homo sapiens
  <220>
  <221> misc feature
  <222> (53)
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  <220>
  <221> misc feature
  <222> (272)
  <223> n equals a,t,g, or c
  <220>
  <221> misc feature
  <222> (275)
  <223> n equals a,t,g, or c
  <220>
  <221> misc feature
  <222> (278)
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  <220>
  <221> misc feature
  <222> (590)
  <223> n equals a,t,g, or c
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  <221> misc feature
  <222> (618)
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 <211> 1690
 <212> DNA
 <213> Homo sapiens
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PCT/US00/05881

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<223> n equals a,t,g, or c
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<221> misc feature
<222> (1664)
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<221> misc feature
<222> (1676)
<223> n equals a,t,g, or c
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agggttttct ggagggcagc aggaaggctg gggaattccc catgtacagt atttatgttt 720
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accagatgac tgcaaaaaaa aaaaaaaaaa aaaaaaaana aaanaaaaa aaaaanaaaa 1680
                                                                1690
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<210> 114
<211> 620
<212> DNA
<213> Homo sapiens
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tgcttgcctg aggtcccact gtgttagtgg gtgggcagga ctggaactcg gttctccaac 480
agcccagage teactettt acacccagag gtggageagg tggettaggg ggtggttatg 540
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<210> 115
<211> 542
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> (392)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (412)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (511)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (521)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (535)
<223> n equals a,t,g, or c
<400> 115
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cototactoc agootocact coggeotoca coatgtoogt caggtgacco agaagtoota 120
caaggtgtee aceteeggee eeegggeett cageageege teetacacca gegggeetgg 180
ctcccgcatc agetegteeg cetteteecg ggtgggegge astteegggg gggeetgaac 240
agcagcatga gtgtggtcgg gggctacggc ggcggggccg gggtatgggg ggcatcacgg 300
ccgtctcagt gaaccagage ctgctgagec cccttwaage tggaatkgga teecaacate 360
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caagetgtge geaacecagg agaaggagea gntcaagace tteaacaaca anttggette 420
gttcatcgac aagtgaagca ctggagcagc agaacaaatt tttggagacc aattggagct 480
tottaaagca gcagaagacg cgcggagaac ntagacaaat nttcgagagt aaatnagaac 540
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<210> 116
<211> 525
<212> DNA
<213> Homo sapiens
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<222> (420)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (424)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (517)
<223> n equals a,t,g, or c
<400> 116
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cgknggccgt tagctgagca atggcgttgg ttaacaacct ggctggtctg gccgtcgtgg 480
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<210> 117
<211> 728
<212> DNA
<213> Homo sapiens
<400> 117
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<210> 118
<211> 948
<212> DNA
<213> Homo sapiens
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<222> (920)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (944)
<223> n equals a,t,g, or c
<400> 118
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<211> 211
<212> DNA
<213> Homo sapiens
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<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (125)
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gengngegag tgtgaggaaa cegeegeete ageegagege gegggeeege ceagggegtt 180
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<210> 120
<211> 1308
<212> DNA
<213> Homo sapiens
<400> 120
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<211> 2516
<212> DNA
<213> Homo sapiens
<400> 121
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<221> misc feature
<222> (1124)
<223> n equals a,t,q, or c
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<211> 1987
<212> DNA
<213> Homo sapiens
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<221> misc feature
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<221> misc feature
<222> (14)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (517)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (1960)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (1204)
<223> n equals a,t,g, or c
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<222> (1226)
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<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> (840)
<223> n equals a,t,g, or c
<400> 128
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<211> 379
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gcagcraagg acccaggggc agagccacgc tggggatgga ccccttcgag gacacgctgc 180
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PCT/US00/05881

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<212> DNA
<213> Homo sapiens
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cccacctgcc gccagagagg acaagagccc atcagaggaa tccgccccca cgacgtcccc 480
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cgtggagtat ctgctcacgg gaattectgg gagccccgag ccggaacacg gttctgtcca 720
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<210> 132
<211> 974
<212> DNA
<213> Homo sapiens
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<222> (165)
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<221> misc feature
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<223> n equals a,t,g, or c
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<221> misc feature
<222> (963)
<223> n equals a,t,g, or c
<400> 132
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<211> 634
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<213> Homo sapiens
<400> 133
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cagtgccctt tccaggcctt aagagaagta aaacttagct gcagcgtcag gaggtggacc 180
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cctacacttg ggcgcacacc ggcagcgatg ccgcacttgc ccctgccgca cwtgcggccg 540
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geoccasegy taccedetat acayeetcas att
<210> 134
<211> 1855
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1818)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (1845)
<223> n equals a,t,g, or c
<400> 134
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cgcgcgcagg ccggcctctg tgtgtgcgcc acagcgagcc ggtgtgcggc agcgacgcca 180
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ggtctgggtt tattgtgtcg gaagatggac tgatcgtgac aaatgcccac gtggtgacca 480
acaagcaccg ggtcaaagtt gagctgaaga acggtgccac ttacgaagcc aaaatcaagg 540
atgtggatga gaaagcagac atcgcactca tcaaaattga ccaccagggc aagctgcctg 600
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geoegtttte cetteaaaac acagteacca eegggategt gageaccace cagegaggeg 720
gcaaagaget ggggeteege aacteagaea tggaetaeat ceagaeegae gceateatea 780
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<210> 135
<211> 917
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (913)
<223> n equals a,t,g, or c
<400> 135
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PCT/US00/05881 WO 00/55173

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tecegetgtt ttettttee ttgeatttte etaatatgee tttactgate egtttgetgt 720
gaaccctatg ttatttccat gtgtcaagtg ggtcttgtgt tgccagcttc tatttgaaga 780
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917
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<211> 1271
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> (1236)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (1255)
<223> n equals a,t,g, or c
<400> 136
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ggcctgtctg cagaatccac ascaaccagc accatgccca tgayactggg gtactggrac 120
atcogcgggc tggcccaykc catcogcctg ctcctggaat acacagactc aagctaygag 180
gaaaagaagt acacgatggg ggacgctcct gattatgaca gaagccagtg gctgaatgaa 240
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tcagaaaagg agcagattcg cgaagacatt ttggagaacc agtttatgga cagccgtatg 420
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gcactccctg aaatgctgaa gctctactca cagtttctgg ggaagcagcc atggtttctt 540
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tcagccccga gctgtccccg tgttgcatga aggagcagca ttgactggtt tacaggccct 1140
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gctcctgcag catggtccct gccttaggcc tacctgatgg aagtaaagcc tcaaccacaa 1200
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<211> 2017
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (295)
<223> n equals a,t,g, or c
<400> 137
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aacaggagat tgctactcta gacaacaaga caatgactga tgtggtgggt aaccararga 180
rgagegeega getgagttet aetteeagee etgggkeagg aggetgtgtg cerataette 240
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<212> DNA
<213> Homo sapiens
<400> 138
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<211> 2759
<212> DNA
<213> Homo sapiens
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<222> (171)
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<221> misc feature
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<223> n equals a,t,g, or c
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<223> n equals a,t,g, or c
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<222> (2746)
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PCT/US00/05881 WO 00/55173

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107

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PCT/US00/05881 WO 00/55173

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PCT/US00/05881

WO 00/55173

113

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PCT/US00/05881

WO 00/55173

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<222> (120)
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<212> DNA
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<213> Homo sapiens

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<212> DNA
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<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (723)
<223> n equals a,t,g, or c
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PCT/US00/05881

WO 00/55173

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<212> DNA
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<222> (889)
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<222> (974) .
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<221> misc feature
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<223> n equals a,t,g, or c
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<221> misc feature
<222> (1077)
<223> n equals a,t,g, or c
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<212> DNA
<213> Homo sapiens
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PCT/US00/05881

WO 00/55173

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<210> 168
<211> 1026
<212> DNA
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<213> Homo sapiens
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<222> (1011)
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129

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<211> 243

<212> DNA

<213> Homo sapiens

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<211> 813
<212> DNA
<213> Homo sapiens
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<223> n equals a,t,g, or c
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tggcccgggg ggaggatgcc agcagcctgc ctatggytgc cagctgtgct gtgagcccag 660
cagcatggcc tgcatctggg aagggacaca ggttgtccag agcccctggc acaactgctg 720
agneanatge tgtggagnea getgttacce tgtaageeac tggcccagea cetgcctaca 780
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813
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<210> 182
<211> 822
<212> DNA
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<221> misc feature
<222> (37)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (49)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (370)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (567)
<223> n equals a,t,g, or c
<400> 182
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<211> 1095
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1082)
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<221> misc feature
<222> (1094)
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<223> n equals a,t,g, or c
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143

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<223> n equals a,t,g, or c
<220>
<221> misc feature
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<222> (590)
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<223> n equals a,t,g, or c
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<213> Homo sapiens
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<221> misc feature
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<221> misc feature
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<222> (5)
<223> n equals a,t,g, or c
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<221> misc feature
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<223> n equals a,t,q, or c
<220>
<221> misc feature
<222> (11)
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<223> n equals a,t,g, or c

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<221> misc feature
<222> (12)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (19)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (1145)
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<211> 688
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> (477)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (684)
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<211> 304
<212> DNA
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<221> misc feature
<222> (269)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (287)
<223> n equals a,t,g, or c
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<211> 417
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> (380)
<223> n equals a,t,g, or c
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<222> (519)
<223> n equals a,t,g, or c
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<211> 1101
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<213> Homo sapiens
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<221> misc feature
<222> (479)
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<222> (428)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (439)
<223> n equals a,t,g, or c
<220>
<221> misc feature
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<222> (449)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (456)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (474)
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aatctggaca tcattttccc tttcagagca tagaatgcag ggggatccag ggaatgggtt 180
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<222> (91)
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<222> (94)
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aagactgaat tgtaagaaaa atctccagcc cttctgtctg cagcttgaga cttgaaccag 180
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<211> 1271
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> (1222)
<223> n equals a,t,g, or c
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cgtggaaaaa tacgagaaac agatcaagca ctttggcatg cttcgccgct gggatgacag 180
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<222> (1007)
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<221> misc feature
<222> (1019)
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1892
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<223> n equals a,t,g, or c
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<223> n equals a,t,g, or c
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 <221> misc feature
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PCT/US00/05881

WO 00/55173

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PCT/US00/05881 WO 00/55173

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<222> (311)
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<211> 2853
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PCT/US00/05881

WO 00/55173

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PCT/US00/05881 WO 00/55173

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gagaacttag agagaagtog gaaaagtttg cottocaago ogaagttaac agaatgatga 420
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<213> Homo sapiens
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<220>

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<211> 3712
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201

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<222> (1791)
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WO 00/55173

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<222> (194)
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<222> (2484)
<223> n equals a,t,g, or c
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211

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PCT/US00/05881

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WO 00/55173 PCT/US00/05881

219

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gaccaggacc ggattccatg gctctgtaac ttgcatgaca ttttactaag agatgtagcc 240
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agttcaaaga tcatggaatc cttcaaaaac atggtccctc agcaagccct tgtgattcga 780
aatggtgaga aaatgagcat aaatgcggag gaagttgtgg ttgggggatct ggtggaagta 840
aaaggaggag accgaattcc tgctgacctc agaatcatat ctgcaaatgg ctgcaaggtg 900
gataacteet egeteactgg tgaateagaa eeceagaeta ggteteeaga ttteacaaat 960
gaaaaccccc tggagacgag gaacattgcc ttcttttcaa ccaattgtgt tgaaggcacc 1020
gcacgtggta ttgttgtcta cactggggat cgcactgtga tgggaagaat tgccacactt 1080
gcttctgggc tggaaggagg ccagaccccc attgctgcag aaattgaaca ttttatccac 1140
atcatcacgg gtgtggctgt gttcctgggt gtgtctttct tcatcctttc tctcatcctt 1200
gagtacacct ggcttgaggc tgtcatcttc ctcatcggta tcatcgtagc caatgtgccg 1260
gaaggtttgc tggccactgt cacggtctgt ctgacactta ctgccaaacg catggcaagg 1320
aaaaactgct tagtgaagaa cttagaagct gtggagacct tggggtccac gtccaccatc 1380
tgctctgata aaactggaac tctgactcag aaccggatga cagtggccca catgtggttt 1440
qacaatcaaa tccatqaaqc tqatacqaca gagaatcaga gtggtgtctc ttttgacaag 1500
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caggctaacc aggaaaacct acctattctt aagcgggcag ttgcaggaga tgcctctgag 1620
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gacgatgtga atttccctat cgataatctg tgctttgttg ggctcatctc catgattgac 2040
cctccacggg cggccgttcc tgatgccgtg ggcaaatgtc gaagtgctgg aattaaggtc 2100
atcatggtca caggagacca tccaatcaca gctaaagcta ttgccaaagg tgtgggcatc 2160
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caggtgaacc ccagggatgc caaggcctgc gtagtacacg gcagtgatct aaaggacatg 2280
acctccgagc agctggatga cattttgaag taccacactg agatagtgtt tgccaagacc 2340
tcccctcagc agaagctcat cattgtggaa aggctgccaa agacagggtg ctatcgtggg 2400
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<211> 505

<212> DNA

<213> Homo sapiens

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258

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PCT/US00/05881

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<221> misc feature

WO 00/55173

261

PCT/US00/05881

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tgcctacaca ttcctactac ccctgggaat tctaactcag atgtgggtag cagcttcctc 120
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aaagagaaac tttttcccag ctgggtgctg tggctcacac ctgtgaatcc cagccctttg 180
gnaggctgna gtgggcagat cgcttgagcc caggagtttg agatcagcct gggcaacatg 240
gtgaantcca tctctgtgaa aaatacaaaa attagccagg tgtggtggtg cgcgcctgtn 300
antcccagct actagggagg ctgaaggtgg gnggnttgnt tnagcccagg aggttgaggc 360
tgcattnggc tgggattcaa accatgttac tccntgacca ngtgngncct ntttcaaann 420
angnaaggga aggggnaagn aaaggaaaag nngnagggng atgccgntnn tngnntngna 480
                                                                   505
gnngnatnan ntaaaaattt ggggg
<210> 329
<211> 559
<212> DNA
<213> Homo sapiens
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<222> (4)
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<222> (343)
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<222> (385)

WO 00/55173

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<222> (445)
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<222> (457)
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<222> (473)
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<220>
<221> misc feature
<222> (503)
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<222> (505)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (551)
<223> n equals a,t,g, or c
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WO 00/55173

264

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<222> (553)
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ttagttgcac tagccatatt tcaaatactt gatggataca tgtggctagt ggctaacata 180
agggatagca cagatataaa acatttcctc ccaaagtgct gggattacag gcatgagcca 240
ccgcgcccgg cctatcatat gaattttgag ggaacacaat catgcagtct gtagcagatg 300
gtaataggct gatatattac acttgttgat gtaanctgga tangtttctt tcttctccaa 360
ggacagettt ttnaatattt aacantneca ttaattttte agttteeggg agaattttat 420
aatttaaaat tgccgactta ngganaancc aattggncca accattacaa tanattttta 480
attccgntta aaaaatccca ccngnggggg aattccgctt aaaattttat tttccattat 540
tcccaatggc ntnaattta
<210> 330
<211> 467
<212> DNA
<213> Homo sapiens
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<222> (99)
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<222> (125)
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<220>
<221> misc feature
<222> (135)
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<220>
<221> misc feature
<222> (138)
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<220>
<221> misc feature
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<222> (145)

265

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<221> misc feature
<222> (263)
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<221> misc feature
<222> (275)
<223> n equals a,t,g, or c
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<222> (298)
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<222> (344)
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<222> (391)
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<220>
<221> misc feature
<222> (393)
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<223> n equals a,t,g, or c

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<222> (402)
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<221> misc feature
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<222> (428)
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<222> (441)
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<222> (458)
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tgtcagtcag tgcgtgaagc caccaccgcc tccggtggna tgaatgcagc ctcccccga 120
ctggncagac accgntgnaa cgggnattat ttcaccctca gagagaggct gatcactatg 180
caaaaacaac tgggaggaaa cccagaagta tattgaatga gcagtgcaga ttagagttgc 240
```

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ccatatcgat gggcancaat tgncaattat tgtgnagcaa tacacacggg gtttccangg 300
gagtnttaaa tgccttaaag taattaaaan ccggggcaat nccnttttac ggatgttttg 360
ctggggtttc cgtttttaac caacattttt ntnggggncc gnccacaaat tttggggttg 420
gnattggncg tttttcttn ntggccccat ttnccngnaa acggggg
<210> 331
<211> 418
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> (37)
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<221> misc feature
<222> (126)
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<221> misc feature
<222> (131)
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<220>
<221> misc feature
<222> (196)
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<220>
<221> misc feature
<222> (202)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (250)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (257)
<223> n equals a,t,g, or c
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<220>

PCT/US00/05881 WO 00/55173

268

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<221> misc feature
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<221> misc feature
<222> (298)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (338)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (344)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (353)
<223> n equals a,t,g, or c
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<222> (380)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (387)
<223> n equals a,t,g, or c
<400> 331
gagetgecaa cetggeaatt antgtetget aagggtnete tttatteace ettaettgga 60
cttcctttcc tgtagggaat ctcacgtaaa atgaaatctt ccctccccca aggtgtccgc 120
aatgtngcca ntgtctgtct gcagattggc tacccaactg ttgcatcagt accccattct 180
atcatcaacg ggtacnaacg antectggcc ttgtctgtgg agacggatta caccttccca 240
cttgctgaan aagtcanggc ttcttggctg atccatctgc cttngtggct gctgccngt 300
tggctgctgc caccacaact gctcctgctg ctgctgcncc ccancttaag ttnaaaccca 360
agaaaatccg aagatccgan aaagatntgg attgggtctc tttgactaat caccaaaa
<210> 332
<211> 486
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
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<222> (9)

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. < 222 > (379)
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 <221> misc feature
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 <221> misc feature
 <222> (486)
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 <400> 332
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 tegetateet gaegetggtg aaegeceegt acaagegagg attttactge ggggatgaet 120
 ccatccggta cccctaccgt ccagatacca tcacccacgg gctcatggct ggggtcacca 180
 teaeggeeae egteateett gteteggeeg gggaageeta eetggtgtae acagaeegge 240
 totattotog otoggactto aacaactacg tggotgctgt atacaaggtg ctggggactt 300
 cctgtttggg gctgccgtga gccagtctct gacagacctg gccaagtaca tgattgggcg 360
 totgaagooc aattotaano gtotgogaao oogattgaao oggtoaatgo togtnatgtg 420
 cagtggagaa gtttgcaggg aacctnttga ttcacgagca gtgtttttaa tcggaatntc 480
 tttgnn
                                                                    486
<210> 333
 <211> 268
 <212> DNA
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PCT/US00/05881

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<213> Homo sapiens
<220>
<221> misc feature
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<222> (69)
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<222> (244)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (260)
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<223> n equals a,t,g, or c

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<220>
<221> misc feature
<222> (263)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (264)
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<400> 333
cccacgctgt ccgatgattt gtcacaatct tatcantaat cattactctg tttttatat 60
ttcaactana agtatcanaa tatagentte cagaaaaacce egaancanag teaetgaeta 120
catcaaagtc tactacacct tgagaaaaca aatgaacgan aatctatttt cctcattcat 180
taccccaaca ataataggac tccctatcgt aattattntc actatgtttc caagcattga 240
tatncccatc acctacccgn ctnntcaa
<210> 334
<211> 517
<212> DNA
<213> Homo sapiens
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<220>
<221> misc feature
<222> (259)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (302)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (332)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (360)
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<220>
<221> misc feature
<222> (410)
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PCT/US00/05881 WO 00/55173

272

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<222> (436)
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<220>
<221> misc feature
<222> (447)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (463)
<223> n equals a,t,g, or c
<220>
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<222> (489)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (496)
<223> n equals a,t,g, or c
<400> 334
cggaaaggag cgcctactaa ggacgccgtc gaggtccggg gcgcctcaac tctatagctc 60
taactggcta gaagtgccca acgtggaatg tttcttttt aaaggcggct cttgaagcga 120
cccggaagcg gaagtggaag aaagttctag tggcttgaga ttaagcctga tcaagatgac 180
aacctcccaa aagcaccgag acttcgtggc agancccatg ggggagaacc agtggggaac 240
ctggctggga ttggtgaant cctgggcaag aaactggaag aaagggtttt gacaaggcta 300
tnttgtcttg gccatttctg gtgctaaaaa anataaaaac tctcccggaa tggtgaaaan 360
ctttttgggc cacccaacat cccgaatgtc cgatgctcca aaatgtgcan cctcttttat 420
gtctttggaa tctctncccc ccccccnatt tgaccaattg ganccccctt cctcaagaaa 480
atgttgttnc ccccanttcc ggttttgatt tccccac
<210> 335
<211> 297
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (19)
<223> n equals a,t,g, or c
<220>
<221> misc feature
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<222> (155)

PCT/US00/05881

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<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (156)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (164)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (166)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (167)
<223> n equals a,t,g, or c
<220>
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<223> n equals a,t,g, or c

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caattcactg gccgtcgttt tacaacgtcg tgacnnggaa aacntnnaat ncttccggct 180
cgtatgttgt gtggaattgt nagcggataa caattcacac aggnancagc tataaccatg 240
attnnnccaa gntcgaaatt aaccntnact aaaggggaca aaagtngggg ctccacg
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<212> DNA
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275

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<223> n equals a,t,g, or c

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277

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  caccactatg taccctggca ttgccgaccg aatgcagaag gagatcacgg ccctagcacc 120
  cagcaccatg aagatcaaga tcattgcccc tccggaggcg caaatactct gtctggatcg 180
  gtggctccat cctggcctct ctgtccacct tccagcagat gtggatcagc aaacagggaa 240
  tacggtgaag ccgggccttc cattgtccac cgcaaatgct ttcttaaaac acttttcctg 300
  gttcctnttc tgtcttttag gcacacaact gtggaatgtn cctgtgggaa tttatggccn 360
  tttcagtttc tttttccaaa tcattcctag ggccaaagtt ttgnattggt tnanccatgg 420
  ggttttttta aataaantnt ggaaataggg ttaattggtt aaaaaaaann nnaaaaaaaa 480
                                                                     506
  ntntggggg gggggcccg ntaccc
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  <211> 623
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  <222> (508)
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  <220>
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  <222> (509)
  <223> n equals a,t,g, or c
  <220>
  <221> misc feature
  <222> (513)
  <223> n equals a,t,g, or c
  <220>
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  <222> (537)
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<222> (599)
<223> n equals a,t,g, or c
<220>
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<222> (612)
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aagaaggagc tgtctgacat cgctcaccgc atcgtggcac ctggcaaggg catcctggct 120
gcagatgagt ccactgggag cattgccaag cggctgcagt ccattggcac cgagaacacc 180
gaggagaacc ggcgcttcta ccgccagctg ctgctgacag ctgacgaccg cgtgaacccc 240
tgcattgggg gtgtcatcct cttccatgag acactctacc agaaggcgga tgatgggcgt 300
cccttccccc aagttatcaa atccaagggc ggtgttgtgg gcatcaaggt agacaagggc 360
gtggtccccc tggcagggac aaatggcgag actaccaccc aagggttgga tgggctgtct 420
gagcgctgtg cccagtacaa ngaaggacgg agctgacttc ggccaagtgg cgttgtgtgc 480
ttaagaatgg gggaacacac cccctcannc ctnggcatca tggaaaatgc caattgntct 540
ggccccgtat gccagtatct ggcancagaa tgcattgggc cattcgggga gtctgananc 600
tcctgatggg ancatgactt gaa
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<211> 344
<212> DNA
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<222> (157)
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<222> (171)
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<222> (210)
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<221> misc feature
<222> (298)
<223> n equals a,t,g, or c
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<222> (317)
<223> n equals a,t,g, or c
<220>
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<222> (330)
<223> n equals a,t,g, or c
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<222> (343)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (344)
<223> n equals a,t,g, or c
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ttttttatat ttcaactaaa agtatcanaa tatagctttc cagaaaaccc cgaaccaaag 120
tcactgacta catcaaagtc tactacacct tggaganaac aaatgaacga naatctattt 180
tecteattea ttaccecaae aataataggn etecetateg taattattat caetatgttt 240
ccaagcatta tattcccatc acctacccga ctaatcaata atcgactcat ctccattnca 300
acaatggatt agtgcantga acatgcaaan gcaaggatta tcnn
<210> 340
<211> 345
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> (6)
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PCT/US00/05881

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<222> (13)
<223> n equals a,t,g, or c
<220>
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<222> (31)
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<222> (88)
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<222> (172)
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<223> n equals a,t,g, or c

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<222> (173)
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<220>
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<222> (343)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (345)
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ggaattcccg ggtcgaccca cgcgtccngn aggaggggac agctgcgggc gcggggaggg 120
ggcgccgngc cgcgnggngc catggnggac agnagagccg ggagtccgag annegggccc 180
gcagcccgag atgtcgccgc catggcttcg ccgcagctct gccgcgcgct ggtgtcggcg 240
caatgggtgg cggaagcgct gcgggccccg cgcgctgggg cagcctctgc agctgntagg 300
acgcctcctg gtnacctggc cggaagctgg ggggcgcgna cgncn
                                                                   345
<210> 341
<211> 170
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (20)
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<220>
<221> misc feature
<222> (23)
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<222> (43)
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<221> misc feature
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<222> (164)
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<222> (170)
<223> n equals a,t,g, or c
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acceacgegt cegeceacgn tenegactag ttetagateg egnaeggeeg etetagagga 60
tccaagctta cttggacatg catgcnacgt catagctctt ctatagtgtc acctaaattc 120
aattcactgg ccgtcgtttt acaacgtcgt gactgggaan atnntaaaan
<210> 342
<211> 387
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> (273)
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<222> (337)
<223> n equals a,t,g, or c
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<222> (351)
<223> n equals a,t,g, or c
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<222> (366)
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<220>
<221> misc feature
<222> (384)
<223> n equals a,t,g, or c
<400> 342
aatgacttgg ttgagtactc accagtcaca gaaaagcatc ttacggatgg catgacagta 60
agagaattat gcagtgctgc cataaccatg agtgataaca ctgcggccaa cttacttctg 120
acaacgatcg gaggaccgaa ggagctaacc gcttttttgc acaacatggg ggatcatgta 180
actogcottg atogttggga accggagotg aatgaagoca taccaaacga cgagogtnac 240
accacgatgc ctgtagcaat ggcaacaacg ttngcaaact attaactggc ggactactta 300
ctctagcttc ccggcaacaa tttatagnct tggtggnggc gggtaaagtt ncaaggccca 360
tttttnggtt tggccttccg gttngtt
<210> 343
<211> 186
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> (26)
<223> n equals a,t,g, or c
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<222> (64)
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<220>
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PCT/US00/05881 WO 00/55173

286

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<222> (152)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (153)
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<221> misc feature
<222> (160)
<223> n equals a,t,g, or c
<220>
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<222> (183)
<223> n equals a,t,g, or c
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tatntcggac ncatctggtg acttccgcaa gctgatggtt gccctggcna aaggttaaaa 120
aacagaagaa tggtccgtcc ttgaatatga anngaatgan ccacatgccc ggatttcctt 180
ganccc
<210> 344
<211> 611
<212> DNA
<213> Homo sapiens
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<222> (11)
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<220>

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cgctctagaa ctagtggatc ccccgggctg caggaattcg gcacgagctg cgttgggctc 120
cgggaagccg ttcgggctgg ggctgtcggc cgcggggcgg aggcactcgc gcgggggatg 180
gcccactgcg tgaccttggt tcagctgtcc atttcctgtg accatctcat tgacaaggac 240
ateggeteca agtetgacce actetgegte ettttacagg atgtnggagg gggeagetgg 300
gctgagcttg gccggactga acgggtgcgg aactgctcaa gccctgagtt ctccaagact 360
ctacagcttg agtaccgctt tgagacagtc cagaagctac gctttggaat ctatgacata 420
gacaacaaga cgccagagct gagggatgat gacttcctag ggggtgctga gtgttcccta 480
ggacagattg tgtccagcca ggtactgact ctccccttga tgctgaagct ggaaaacctg 540
ctgggcgggg gaccatcacg gtctcagctc aggaattaaa ggacaatcgt gtagtaacca 600
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tggaggtaga g
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<212> DNA
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<220>
<221> misc feature
<222> (289)
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<221> misc feature
<222> (296)
<223> n equals a,t,g, or c
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<222> (329)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (331)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (342)
<223> n equals a,t,g, or c
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tttccttcta cagtattcct gaatttgacg aatggaaaaa acatatagaa aaccagaaag 60
cctggaaaat aaagtactat aaaggattgg gtactagtac agctaaagaa gcaaaggaat 120
attttgctga tatggaaagg catcgcatct tgtttagata tgctggtcct gaagatgatg 180
```

```
ctgccattac cttggcattt agtaagaaga agattgatga cagaaaagaa tggttaacaa 240
attttatgga agaccggaga cagcgtagct acatggctta ccagaggant gattcnctct 300
caactcagac atgaaagatc tataccacnc ntgttgatgg cntt
<210> 346
<211> 506
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (392)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (452)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (453)
<223> n equals a,t,q, or c
<220>
<221> misc feature
<222> (472)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (480)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (495)
<223> n equals a,t,g, or c
<400> 346
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tgggattggt cttcttttt cttcagtgag ttttttcccc aacaggttct gatggtcctt 120
tggctaccag caaaccagtc cctgcagaaa agtcaggtct tccagtgggt cctgagaacg 180
gagtagaact ttccaaagag gagctgatcc gcaggaagcg cgaggagttc attcagaagc 240
atgggagggg tatggagaag tccaacaagt ccacgaagtc agatgctcca aaggagaagg 300
gcaaaaaagc accccgggtg tgggaactgg gtggctgtgc taacaaagaa atgttggatt 360
acagtacttc caccaccaat ggaacccctg angettgect tgtctgagga cattaacctt 420
gattccaagg gactgggtct ggggggcact tnnggatctg gactgcacac tntgatgacn 480
                                                                   506
aagggcttgt taaantttcc aaacta
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<210> 347

PCT/US00/05881 WO 00/55173

289

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<211> 444
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<213> Homo sapiens
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<222> (289)
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gctacgattt cagagtaccc tggtaatagc tgagcatgca aatgattccc tagcacccat 120
tactttaaat accattactg cagccacacg ccttggaggt gaagtgtcct gcttagtagc 180
tggaaccaaa tgtgacaagg tggcacaaga tctctgtaaa gtagcaggca tagcaaaagt 240
tctggtggct cagcatgatg tgtacaaagg cctacttcca gaggaactna caccattgat 300
tttggcaact cagaagcagt tcaattacac acacatctgt gctggagcat ctgccttcgg 360
aaagaacctt ttgcccagag tagcagccaa acttgaggtt gccccgattt ctgacatcat 420
                                                                   444
tgcaatcaag tcacctgaca catt
<210> 348
<211> 358
<212> DNA
<213> Homo sapiens
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<222> (19)
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<222> (187)
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<220>
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<221> misc feature

<223> n equals a,t,g, or c

WO 00/55173 PCT/US00/05881

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agctggnaaa aggggtgatt gttgcaaaga gcaaagaaga ggcctgcaag ctgtacaaga 240
gatcatgcag gtaggctggg tcttctggaa aaatttactn ttgtattcat actgnatgaa 300
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PCT/US00/05881 WO 00/55173

291

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tgctgcagtg gtatgagccg ctgcagaagt ttctgctgct gaagaacttc tccagccctc 180
tgcccanccc agctgggatg ctgganccgc tggtgctgga tgggaaggag ctgccgcagn 240
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PCT/US00/05881 WO 00/55173

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cgtgggcaac cgggtgtaca tgccctgcct gtatgtttat aacaaaatcg accagatctc 180
catggaagag gtggaccgcc tggcccgaaa acccaacagt gtggtcatca gctgcggcat 240
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ggcctcagtg gagcacgtgg gcaccagcac caagtacagt ccgcagcggg tgggcctgac 420
ccacaccatg gagcatgagg acgtcatcca gatcgtgaag aagtaacggc gcctgccggg 480
cetteegeee acetgetegt etecettggg aggtggteee actgggacae acaaacacee 540
aaacagaaaa atacaaatac acgtacccca agaaggggtc cctcaagtct ctgctattta 600
cagaagtttc ttcagtangc agaccaaaaa tgtgttgggc aaaagggctc ggntggangc 660 '
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ggtgaggetc agattgegtc catcagecag agtgtggege gtttetnetc tgcatcegge 180
gtggaggtgg acaaggtcgt tgaagccttc gaggggggcc cgtacccatt tgcctatagt 240
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WO 00/55173

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acaccatctt taagaaccgt aatactcacc gcaagggtct gcaacttcat tcttgaagtc 240
agtgaggcca agaacccatc aattccgtac acatttnggt gactttgaag agactgtcac 300
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tcaccaageg gtgagactat cacctatege caagtggtee taagtgtgaa egtgaagtee 420
ccagccctgc tgctgagcca gttgctgccc tacatggaga acaagaaggg tgctgtcatn 480
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ccttcaacat gccggaacca gcgaagtccg ctcccgcgcc caagaagggc tcgaagaaag 180
ccgtgactaa ggcgcagaag aaggacggca agaagcgcaa ggnanccgca aggagagcta 240
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ggccatggga atcatgaact ccttcgtcaa cgacatcttc gaacgcatcg cgggtgaggc 360
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cgtgcgcctg ctgctgcccg gggagttggc caagcacgcc gtgtccgagg gcaccaaggc 480
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gcaatctcat cactggaatg ttccagcgac tggacaagct gaggaagaat gccttcgcca 240
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gccaggagct tgcctttccg ctgagtccag attggcaagt ggactacgaa gtcatacaca 360
tggcggaaac tggatctggc aagcgaggag acccanacgc tggttcgaga gtacttttnc 420 ·
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WO 00/55173

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gaaccccgtg gaacagaggc agcgcatcat cggagggcaa aaagccangg ggatagtggg 180
ggcgtttttg cagtaaggga cccgaacact gatcgctggg tggccacggg catcgtgtnc 240
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tggccttgga tcaagnnaga cctngganca ggaggactnc cgccccanca ttcactaggt 360
tecnaateea gngageagtt tegeanaaan canecanaca canetteece etntttngnn 420
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aatgcgaatg ggcagcgact acatccgtga gtggaatgtg gtgaagtttg cccgtntcgg 240
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ccttatttgg tttccncagg atggtggatg cccgagaant ttttggaaaa cccacgttgn 360
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 taaatttttt gctgacctgc tggattacat caaaggactg antagnaaat agtgnataga 180
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gtttgaggta cataagaaaa atgtaagggg tgaattcact tattatgaaa tacaagataa 180
tacagggaag atggaagtgg tggtgcatgg acgactgacc acaatcaact gtgaggaagg 240
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gagatetgta atteatagte acateaaggt cateaagace aggaaaaaca agaaagacat 360
actcaatcct gattcaagta tggaaacttc accagacttt ttcttctaaa atctggatgt 420
cattgacgat aatgtttatg gagataaggt ctaagtgcct aaaaaaaatgt acatatacct 480
ggttgaaata caacactata catacacac ancatatata ctagcttgtt aatcctatgg 540
aaatggggta tntggagnnc ttttttaatt tttcatagnt ttttttnat aanaatggca 600
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caccattacc ageggeggea atceteegge etttteeetg acaceggaeg gaaagetgae 60
cgctaaaaat gcggatatca gtggcagtgt gaatgcgaac tccgggacgc tcagtaatgt 120
gacgataget gaaaactgta egataaacgg tacgetgagg geggaaaaaa tegtegggga 180
cattgtaaag gcggcgagcg cggcttttcc gcgccaggtg gaaagcagtg tggactggcc 240
gtcaggtacc cgtactgtca ccgtgaccga tgaccatcct tttgatcgcc agatagtggt 300
gcttccgctg acgtttcgcg gaagtaagcg tactgtcagc ggcaggacaa cgtattcgat 360
gtgttatctg aaagtactga tgaacggtgc ggtgatttat g
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accegaacae ggeactggte ggegtgeagg tggactegga geagttegge agceageagg 60
tgagccgtaa ttatcatctg cgcgggcgta ttctgcaggt gccgtcgaac tataacccgc 120
agacgeggea atacageggt atetgggaeg gaacgnttaa aceggeatae ageaacaaca 180
tggcctggng tctgtgggat atgctgaccc atccgcgcta cggcatgggg aaacgncttg 240
gtgcggcgga tgtggataaa tgggcgctgt atg
<210> 362
<211> 248
<212> DNA
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cgaatcccat ctcngcaagg agctgctgga aaaagtcgag ctgacggagg ataacgccag 120
cagactggag gagttttcga aagantggaa ggatgccagt nataagtgga atgccatgtg 180
ggctntcaaa attnagcaga ccaaagacgn caaacgantt ttattctgct atttagtagt 240
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248
aagatcag
<210> 363
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<212> DNA
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<222> (137)
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<222> (145)
<223> n equals a,t,g, or c
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atctggaggc gacggggctg tatcaggtgc cgttgtcagc ggcacagccg ggcgatgtgc 120
tgctgtgctg ntttggntca tcanngncg
<210> 364
<211> 352
<212> DNA
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<222> (340)
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gcanaaagaa aatggcacag taacagctgc caatgccagt acactgaatg atggagcagc 60
tgctctggtt ctcatgacgg cagatgcagc gangaggctc aatgttacac cactggcaag 120
aatagtagca tttgctgacg ctgctgtaga acctattgat tttccaattg ctcctgtata 180
tgctgcatct atggtnctta aagatgtggg attgaaaaaa gaagatattg caatgtggga 240
agtaaatgga agcctttagt ctggttgtac tagcaaacat taaaaatgtt ggagattgga 300
tccccaaaaa gtgaatatnc anggnaggag ctgtttcncn ggggacatcc ca
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310
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ggcttgtgcc gctgctggan tgacagcctt ncgaggcttt gctgtctcgg cacggnaggt 120
ctggcaaacc anggacagac caggnacatg ggaccaaagc cggaacctcc tgctcaacgg 180
gaagteetan eecaccaaag tgegeetgat etggggggge teeetneece cagteaageg 240
                                                                   272
gncggcggat gaactggatn nacgccccgg at
<210> 366
<211> 254
<212> DNA
<213> Homo sapiens
<220>
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<220>
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<222> (208)
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<221> misc feature
<222> (209)
<223> n equals a,t,g, or c
<220>
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<222> (236)
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<223> n equals a,t,g, or c

WO 00/55173 PCT/US00/05881

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<222> (244)
<223> n equals a,t,g, or c
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ggctctacta ggactcacta tanggaaagc tggtacgcct gcaggtaccg gtccggaatt 60
cccgggtcga cccacgcgtc cgcttctctg cctagaaggg ataatattat cactcttcgt 120
tataataaca atcaccatct taattaacca ccttacatta gccagcataa cccctatcat 180
ccttcttgta tntgcagcct gtgaagenne actggggett atccctttta gttatnatct 240
caantacata cgga
<210> 367
<211> 185
<212> DNA
<213> Homo sapiens
<400> 367
gattggattc gacaacaaaa aagacctgct tatctcggtg ggcgatttgg ttgatcgtgg 60
tgcagagaac gttgaatgcc tggaattaat cacattcccc tggttcagag ctgtacgtgg 120
aaaccatgag caaatgatga ttgatggctt atcagagcgt ggaaacgtta atcactggct 180
gctta
                                                                    185
<210> 368
<211> 458
<212> DNA
<213> Homo sapiens
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<222> (27)
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PCT/US00/05881 WO 00/55173

313

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<222> (232)
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<220>

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ccggagtgag ccttgaacgc ctggacctgg acctcacagc tgacagccag ccacccgtct 120
tcaaggtctt cccaggcagt accactgagg actacaacct tattgttatn gaacgtggcg 180
ctgccgctgc acnaccggcc agccagggac tgcgcctgca ggaacccctg gngccccacc 240
cctggntggn atggccattg tcaaggagga ggagacggag gctgccattg gagcccctcc 300
tactgccact gagggncctg agaccaaacc tgtgcttatn gctcttgagg agggtcctgg 360
tgctgagggt tcccggctgg actcactagt ggcanaacna ctcnggctgg aagtngtagc 420
tctgagggac tcngccccag tgttggccgg gacctgat
<210> 369
<211> 288
<212> DNA
<213> Homo sapiens
<220>
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<222> (15)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (17)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (47)
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<222> (56)
<223> n equals a,t,g, or c
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<220>
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<222> (225)
<223> n equals a,t,g, or c
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<222> (239)
<223> n equals a,t,g, or c
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gcgctqqagc tgctngngca ctgcggcgtg tgcagagagc gcctgcnacc cgaganggag 60
ccccgcctgc ngccctgttt gcactcggcc tgtagtgcct gcntagggcc cgcngccccg 120
ccgccgccaa cagctcgggg gacggcgggg cggcgggcga cggcaccgtg gtggactgtc 180
ccgtgtgcaa gcaacagtgc ttctccaaag acatcgtgga gaatnatttc atgcgtgana 240
gtggcagcaa ggctgccacc gacgcccagg atgcgaacca gtgctgca
<210> 370
<211> 292
<212> DNA
<213> Homo sapiens
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<223> n equals a,t,g, or c

WO 00/55173 PCT/US00/05881

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<222> (101)
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<220>
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<222> (141)
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<221> misc feature
<222> (263)
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ccatctttgc attgttcctc atccgcctcc ttgctcgccg cagccgnctc cgncgcgcgn 60
ntcctccgcc gccgcggact ccggcagctt tatcgccaga ntccctgaac tctcgctttc 120
tttttaatcc cctgcatcgg ntcaccggcg tgccccacca tgtcagacgc agccgtagac 180
accageteeg aaateaceae caaggaetta aaggagaaga aggaagtttt ggaaagagge 240
agaaaatgga agagacggcc ctncttaacg gggaatgcta atttagggaa at
<210> 371
<211> 477
<212> DNA
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<222> (276)
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<222> (313)
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<221> misc feature
<222> (374)
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<222> (427)
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<222> (434)
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<221> misc feature
<222> (447)
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<221> misc feature
<222> (448)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (451)
<223> n equals a,t,g, or c
<400> 371
ggcacaggat aattttaagc atttaaatgg aattnatctt tttcactgta ttgatccaaa 60
tggttccaag cataaaagaa cggacagatc aattttatgt tgtttacgaa aaggagaatc 120
tggccagtca tggcaagggt taacaaaaga aagggcaaag cttaattggc ttagtgtcga 180
cttcaataat tgggaaagac tgggaagatg attcaaatga agacatgtct aattttgaat 240
cgtttctctg aggattcaca agacagtgat gatggnaaaa atgccagatc tgggagtaag 300
ggaatattgt contcacctg ggtttttgag gaaaggaaaa tnaactttct ctggcaaggt 360
tttccataat ttgngaggaa ttccccgagt ttgttagcnc ctaaagggcn gttatgctcg 420
tatttgnccc actntaaccc ctttttnnca nccggtttgt ttttttaaaa gggcttc
<210> 372
<211> 443
<212> DNA
<213> Homo sapiens
<220>
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<222> (67)
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<222> (174)
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<222> (220)
<223> n equals a,t,g, or c
<220>
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<222> (222)
<223> n equals a,t,g, or c
<220>
<221> misc feature
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PCT/US00/05881 WO 00/55173

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319
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<222> (293)
<223> n equals a,t,g, or c
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<222> (314)
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<221> misc feature
<222> (329)
<223> n equals a,t,g, or c
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<222> (335)
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<222> (340)
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<222> (364)
<223> n equals a,t,g, or c
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<222> (373)
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<220>
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<222> (411)
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PCT/US00/05881 WO 00/55173

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agaaganatc cttnaccct gtaggaatgt ttttgaaact aaatttnatg aacgtnaaat 120
ttnccagtgg ttattatgaa cttccttgtc gaagttgaaa ggtgaacaac nctnatattg 180
caaataccgt agagetteag agtgeaagat tetecaetgn angttgggea tteacaaatg 240
ttggatcttt cccaccgtgg gatgaagggt tcagaggcat tgcacccaaa atnacccggg 300
tgaacatacc cagnccaaag cccaggggna cattnatcgn ggacaggccc nccagaattt 360
ggcntgttct ttnccagttg gtaggtgtgg aacttggggt tgaattnatt ncttaaccga 420
attttnccgn ttccttaacc gag
<210> 373
<211> 464
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (20)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (235)
<223> n equals a,t,g, or c
<400> 373
cggatccgca ggcgcacgtn gcgatgttgt cctctacagc catgtattcg gctcctggca 60
gagacttggg gatggaaccg cacagagccg cgggcccttt gcagctgcga ttttcgccct 120
acgttttcaa cggaggtact atactggcaa ttgctggaga agattttgca attgttgctt 180
ctgatactcg attgagtgaa gggttttcaa ttcatacgcg ggatagcccc aaatnttaca 240
aattaacaga caaaacagtc attggatgca gcggttttca tggagactgt cttacgctga 300
caaagattat tgaagcaaga ctaaagatgt ataagcattc caataataag gccatgacta 360
cgggggcaat tgctgcaatg ctgtctacaa tcctgtattc aaggcgcttc tttccatact 420
atgtttacaa catcatcggt ggacttgatg aagaaggaaa gggg
<210> 374
<211> 369
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (216)
<223> n equals a,t,g, or c
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321

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<221> misc feature
<222> (218)
<223> n equals a,t,g, or c
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<223> n equals a,t,g, or c
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<222> (221)
<223> n equals a,t,g, or c
<220>
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<222> (332)
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<222> (360)
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<222> (363)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (369)
<223> n equals a,t,g, or c
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ggcacagcct ctacagccat gtattcggct cctggcagag acttggggat ggaaccgcac 60
agageegegg geeetttgea getgegattt tegeeetaeg ttttcaaegg aggtactata 120
ctggcaattg ctggagaaga ttttgcaatt gttgcttctg atactcgatt gagtgaaggg 180
ttttcaattc atacgcggga tagccccaaa tgttgncnna ntaacagaca aaacagtcat 240
tggatgcagc ggttttcatg gagactgtct tacgctgaca aagattattg aagcaagact 300
aaagatgtat aagcattcca ataataaggc cntgactacg gggggcaatg ctggcangcn 360
gtnctacan
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<210> 375

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<211> 313
<212> DNA
<213> Homo sapiens
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<223> n equals a,t,g, or c
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<221> misc feature
<222> (249)
<223> n equals a,t,g, or c
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<222> (259)
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<222> (293)
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<222> (308)
<223> n equals a,t,g, or c
<400> 375
taccetteat cactaaagge egeetgtgeg tnttttttta egggattttt ttatgtegat 60
gtacacaacc gcccaactgc tggcggcaaa tgagcagaaa tttaagtttg atccgctgtt 120
totgogtoto tttttccgtg agagetatec ettcaccacg gaggaaagte tatetetcac 180
aaattccggg actggtaaac atggcgctgt acgtttcgcc gattgtttcc ggtgaaggtt 240
atcccgttnc cctggcggnt tccacctntg aatttaaggc cgggataatg tcnaagcccg 300
                                                                   313
aagcatgnaa gtg
<210> 376
<211> 375
<212> DNA
<213> Homo sapiens
<400> 376
cgggttccgg tgaccacgaa ggcggcaaag gcgacggaat ggaggaggtg cctcacgact 60
gtccaggggc cgacagcgcc caggcgggca gaggggcttc atgtcaggga tgccccaacc 120
ageggetgtg egettetgga gegggggeea eteeggacae ggetatagag gaaatcaaag 180
```

323

```
agaaaatgaa gactgtaaaa cacaaaatct tggtattgtc tgggaaaggc ggtgttggga 240
aaagcacatt cagcgcccac cttgcccatg gcctagcaga ggatgaaaac acacagattg 300
ctcttctaga catcgatata tgtgggccat cgattcccaa gataatggga ttggaaggag 360
agcaggttca ccaga
<210> 377
<211> 434
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (9)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (17)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (22)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (32)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (33)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (47)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (58)
<223> n equals a,t,g, or c
<220>
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<222> (64)
<223> n equals a,t,g, or c
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<220>

324

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<222> (112)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (116)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (118)
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<220>
<221> misc feature
<222> (146)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (151)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (161)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (163)
<223> n equals a,t,g, or c
<220>
<221> misc feature
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PCT/US00/05881

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<222> (193)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (212)
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<220>
<221> misc feature
<222> (214)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (228)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (235)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (243)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (250)
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<220>
<221> misc feature
<222> (262)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (263)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (264)
<223> n equals a,t,g, or c
<220>
<221> misc feature
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<222> (265)

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<220>
<221> misc feature
<222> (267)
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<220>
<221> misc feature
<222> (279)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (301)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (320)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (330)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (337)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (351)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (370)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (381)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (409)
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<223> n equals a,t,g, or c

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<400> 377
ggcacgagng tggctcnagg gngtcacctt cnntgttacc accgttnaca ccaaaagncg 60
gacngagana gtncagaagc tgtgcccagg ggggcagntc ccattcctgc tntatngnac 120
tgaagtgcac acagacacca acaagnttgc ngaatttctg nangcagtgc tgtgccctcc 180
caggtacccc aanctggcag ctctgaaccc tnantccaac acagctgngc tgganatatt 240
tgncaaattn tctgcctaca tnnnnanttc aaacccagna ctcaatgaca atctggagaa 300
nggactectg aaaqeeetgn aegttttagn caattantta acateeeccc netcagaaga 360
agtggatgan accagtgctg nagtgaaggt gtctctcaga agaagtttnt ggatagcacg 420
agctcáccct gggg
<210> 378
<211> 506
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (133)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (294)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (367)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (376)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (386)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (389)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (421)
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<223> n equals a,t,g, or c

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<220>
<221> misc feature
<222> (440)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (443)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (472)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (479)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (492)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (493)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (496)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (503)
<223> n equals a,t,g, or c
<400> 378
aattttcact cccctcagaa cataacatag taaatggatt gaattatgaa gaatggtttt 60
tatgcgactt accgcagcaa aaataaaggg aaagataagc gctcaataaa cctgtctgtt 120
ttccttaatt ctntgctggc tgataatcat cacctgcagg ttggctccaa ttatttgtat 180
attcataaaa tcgatggaaa aacttttctc tttaccaaaa caaatgacaa gagtctggtt 240
cagaagataa atcgctctaa agcttcagtt gaagatatta agaacagcct cgtngatgac 300
ggaatcattg ggattcccat ctttttgtt tgttgaaggc gacaccattg gtttttgcca 360
gaactgnttt tcgggncggc cacatncgnt tttgacaggt ttttttaatc ggggaaggga 420
ntgtccttaa ggcgtggggn gcngttcagt tggggccctg ttggggggac cnccaaggng 480
gtggttatgg cnnggntttc atnggc
```

PCT/US00/05881

WO 00/55173

<223> n equals a,t,g, or c

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<210> 379
<211> 550
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (6)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (9)
<223> n equals a,t,g, or c
<400> 379
gacganacna acceteacta aagggaacaa aagetggage tecacegegg tgeggeeget 60
ctagaactag tggatccccc gggctgcagg aattcggcac gaggccatcc agactgagga 120
agacceggaa acttagggge caegtgagee aeggeeaegg eegcatagge aageaeegga 180
agcaccccgg cggccgcggt aatgctggtg gtctgcatca ccaccggatc aacttcgaca 240
aataccaccc aggctacttt gggaaagttg gtatgaagca ttaccactta aagaggaacc 300
agagettetg eccaactgte aacettgaca aattgtggae tttggteagt gaacagacae 360
gggtgaatgc tgctaaaaac aagactgggg ctgctcccat cattgatgtg gtgcgatcgg 420
gctactataa agttctggga aagggaaagc tcccaaagca gcctgtcatc gtgaaggcca 480
aattetteag cagaagaget gaggagaaga ttaagagtgt tgggggggcc tgtgtcctgg 540
                                                                   550
tggcttgaag
<210> 380
<211> 573
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (4)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (6)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (10)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (160)
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WO 00/55173

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<400> 380
aagnenagan agccaaccet cactaaaggg aacaaaaget ggageteeac egeggtgegg 60
ccgctctaga actagtggat cccccgggct gcaggaattc ggcacgagcg caaagaaggg 120
tggcgagaag aaaaagggcc gttctgccat caacgaaggn taacccgaga atacaccatc 180
aacattcaca agcgcatcca tggagtgggc ttcaagaagc gtgcacctcg ggcactcaaa 240
gagattegga aatttgecat gaaggagatg ggaacteeag atgtgegeat tgacaceagg 300
ctcaacaaag ctgtctgggc caaaggaata aggaatgtgc cataccgaat ccgtgtgcgg 360
ctgtccagaa aacgtaatga ggatgaagat tcaccaaata agctatatac tttggttacc 420
tatgtacctg ttaccacttt caaaatttct gtgctaaaca gtgttacagt cgccaagagc 480
ccataaaggg agccctcctg gaagtggatg aggccttggg teteggetet teattgette 540
ctgagctgca gcagatgcct ttacaaccaa gct
<210> 381
<211> 531
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (5)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (8)
<223> n equals a,t,g, or c
<400> 381
gcagnacnaa ccctcactaa agggaacaaa agctggagct ccaccgcggt gcggccgctc 60
tagaactagt ggatcccccg ggctgcagga attcggcacg aggcggcgtt ggcggcttgt 120
gcagcaatgg ccaagatcaa ggctcgagat cttcgcggga agaagaagga ggagctgctg 180
aaacagctgg acgacctgaa ggtggagctg tcccagctgc gcgtcgccaa agtgacaggc 240
ggtgeggeet ccaagetete taagateega gtegteegga aatecattge eegtgttete 300
acaqttatta accagactca gaaagaaaac ctcaggaaat tctacaaggg caagaagtac 360
aagcccctgg acctgcggcc taagaagaca cgtgccatgc gccgccggct caacaagcac 420
gaggagaacc tgaagaccaa gaagcagcag cggaaggagc ggctgtaccc gctgcggaag 480
tacgcggtca aggcctgagg ggcgcattgt caataaagca cagtggctga g
<210> 382
<211> 300
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)
<223> n equals a,t,g, or c
<220>
<221> misc feature
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<222> (5)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (40)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (43)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (59)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (171)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222× (172)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (175)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (179)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (184)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (190)
<223> n equals a,t,g, or c
<220>
<221> misc feature
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<222> (203)

PCT/US00/05881 WO 00/55173

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<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (271)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (292)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (293)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (300)
<223> n equals a,t,g, or c
<400> 382
ngggngtacc acaaatataa ggcaaagagg aactgctggn cangagtacg gggtgtggnc 60
atgaatcctg tggagcatcc ttttggaggt ggcaaccacc agcacatcgg caagcctcc 120
accatccgca gagatgcccc tgctggccgc aaagtgggtc tcattgctgc nngcnggant 180
ggangtoton ggggaaccaa gantgtgcag gagaaagaga actagtgctg agggcctcaa 240
taaagtttgt gtttatgcca aaaaaaaaa naaaaaaaaa aaaaaaaaa annaaagagn 300
<210> 383
<211> 475
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (36)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (146)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (363)
<223> n equals a,t,g, or c
<220>
<221> misc feature
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<222> (367)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (401)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (404)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (415)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (450)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (451)
<223> n equals a,t,g, or c
<400> 383
atgacgccgg tgcagcgggg gggcccgggg gcctgngtgg ccctgggatg gggaaccgcg 60
gtggcttccg cgaggtttcg gcagtggcat ccggggccgg ggtcgcggcc gtggacgggg 120
ccggggccga ggccgcggac tcgcgnaggc aaggccgagg ataaggagtg gatgcccgtc 180
accaagttgg gccgcttggt caaggacatg aagatcaagt ccctggagga gatctatctc 240
ttctccctqc ccattaagga atcagagatc attgattctt cctgggggct ctctcaagga 300
tgagttttga agatatgcca tgcagaagca gaccctgccg gccacgcacc agttcaagca 360
ttnttgnaac gggattaaat gccactcgtt tggtttaatg nccnagagtg gcacncatcc 420
tgggcaaaac tggcaaattt caagteettn naagtatggg gaaaatggaa eecaa
<210> 384
<211> 127
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (5)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (8)
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334

<223> n equals a,t,g, or c <220> <221> misc feature <222> (31) <223> n equals a,t,g, or c <220> <221> misc feature <222> (62) <223> n equals a,t,g, or c <220> <221> misc feature <222> (71) <223> n equals a,t,g, or c <220> <221> misc feature <222> (103) <223> n equals a,t,g, or c <220> <221> misc feature <222> (124) <223> n equals a,t,g, or c<400> 384 caatntgnag accagattcc taaggctgca naggggacag tgggatctat tttaggaccg 60 angagattaa ncagagacac aggcaattgt atgtcagcag ctngatttaa cccacctaaa 120 127 aggngcg <210> 385 <211> 317 <212> DNA <213> Homo sapiens <220> <221> misc feature <222> (30) <223> n equals a,t,g, or c <220> <221> misc feature <222> (151) <223> n equals a,t,g, or c <220> <221> misc feature <222> (187)

<223> n equals a,t,g, or c

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<220>
<221> misc feature
<222> (203)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (231)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (264)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (308)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (311)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (316)
<223> n equals a,t,g, or c
<400> 385
ggcacgaggg atgtgcgacg tgtgcctggn gtagccccga ctcttgtacg gtcggcatct 60
gagaccagtg agaaacgccc cttcatgtgt gcttacccag gctgcaataa gagatatttt 120
aagctgtccc acttacagat gcacagcagg naagcacact ggtgagaaac cataccagtg 180
tgacttnaag gactgtgaac gangttttct cgttcagacc agctcaaaag ncaccaaagg 240
aggacataca ggtgtgaacc attnccagtg taaaattgtt cagcgaaatt ctcccggtcc 300
                                                                   317
gaccaacnga ngaccna
<210> 386
<211> 433
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (295)
<223> n equals a,t,g, or c
<220>
<221> misc feature
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WO 00/55173

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<222> (311)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (359)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (385)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (405)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (407)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (427)
<223> n equals a,t,g, or c
<400> 386
tttcaaaagc tatttaggtg acactataga aggtagcctg caggttaccg gtccggaaat 60
tcccgggtcg acccacgcgt ccgccgagag ccttagccga cggaaactgg acactggaac 120
eggeagegee atgagactee tecceegett getgetgett etettaeteg tgtteeetge 180
cactgtcttg ttccgaggcg gccccagagg cttgttagca gtggcacaag atcttacaga 240
ggatgaagaa acagtagaag attccataat tgaggatgaa gatgatgaag ccgangtaga 300
agaagatgaa nccacagatt ttgtagaaga taaagaggaa gaagatgtgt ctggtgaanc 360
tgaaacttta ccgagtgcag atacnactat actgttttta aaggngnaga ttttccgcca 420
                                                                   433
ataacantgt gaa
<210> 387
<211> 407
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (315)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (356)
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<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (359)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (373)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (376)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (407)
<223> n equals a,t,g, or c
<400> 387
atttgaagca aacaggcagc gcgcgacaat ggcggtcgct cgtgcagctt tgggggccatt 60
ggtgacgggt ctgtacgacg tgcaggcttt caagtttggg gacttcgtgc tgaagagcgg 120
gettteetee eccatetaca tegatetgeg gggeategtg tetegaeege gtettetgag 180
tcaggttgca gatattttat tccaaactgc ccaaaatgca ggcatcagtt ttgacaccgt 240
gtgtggagtg ccttatacag ctttgccatt ggctacagtt atctgttcaa ccaatcaaat 300
tccaatgctt attanaagga aagaaacaaa ggattatgga actaagcgtc ttgtanaang 360
aatattaatc canganaaac tgtttaatca ttgaaatgtt gtcccan
<210> 388
<211> 244
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (215)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (221)
<223> n equals a,t,g, or c
<400> 388
ttcgttcatc tatcggatcg ccacactcac aacaatgagt ggcagatata gcctggtggt 60
traggragge cattitiatt grigitige grigitaatte tietattiet gaigetgaat 120
caatgatgtc tgccatcttt cattaatccc tgaactgttg gttaatacgc ttgagggtga 180
atgcgaataa taaaaaagga gcctgtagct ccctnatgat nttgcttttc atgttcatcg 240
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338

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ttcc
<210> 389
<211> 239
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (21)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (55)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (64)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (71)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (116)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (128)
<223> n equals a,t,g, or c
<220>
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ctgncgcccg ncgtgatgcc agggaagaca gggcgacctg gaagtccaac tacttnctta 120
agatcatnca acgtattggg atgattatcc taaaatgggt tcnattggtg ggtagcgagt 180
acganatggt ggggcntcct anagntagta tggcgagcta gagtcccggc taatgttcc 239
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<222> (374)
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cgcgctgcnc gcacactgag gccgccggg acaaagcccg gnntcggngc gacctttggt 120
cccggnctca gtgagcgagc gagcgcgcag agagggagtg gccaacttna tcactagggg 180
ttccttgtag tnaatgatta accegccatg ctacttngnc nacgtagcca tgggntacca 240
agetegaget etetagaete gaegegegta ataegaetea etatagggeg aatttgaget 300
ccaccgcggt tgcggccgct ctactagagt cgacctcatg gnttnncccc gaaacccgcn 360
aacacccgct gacncgccct ta
<210> 391
<211> 375
<212> DNA
<213> Homo sapiens
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<223> n equals a,t,g, or c
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<222> (70)
<223> n equals a,t,g, or c
<220>
<221> misc feature
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PCT/US00/05881

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<222> (117)
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<222> (208)
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<221> misc feature
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<222> (279)
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PCT/US00/05881 WO 00/55173

343

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cgggtgcagn tgccagggtg gcctgagcga tctacggatg ggcngtatgg agtggangag 120
acgagatgcg ggtgttanag cagggnctga ccggagtgnc acacatgagt gtcaggtgca 180
ggtagtccga gtcggcgaca tgagcctnga gtagagtcat cantcgatga gatctggagg 240
caactggcga gcaagaccgt ntggtgcant gtcantcang ctgttgcagg tgagagcant 300
gcactcgtcg agtggcgaga cagatcaatc tctgttagcg ggtggaggtt ncactcgcgc 360
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<221> misc feature
<222> (13)
<223> n equals a,t,g, or c
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atcgtgnttc ctgtccattg gactgtaagg tttatgtagg catcttggga acnatggnan 120
                                                                    121
<210> 393
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<221> misc feature
<222> (70)
<223> n equals a,t,g, or c
<220>
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<222> (73)
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<400> 393
83
aaaanncccn ggngggggcc ccc
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<220>
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<222> (13)
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<221> misc feature
<222> (64)
<223> n equals a,t,g, or c
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aggneetegg teagegactg gatgetegee ateaaggtee agtggaagtt etteaagagg 120
aaaggegeee eegeeceagg etteegegee eagegetege eaegeteagt geeegtttta 180
                                                         218
ccaataaact gagcgacccc aaaaaaaaaa aaaaaaag
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<211> 83
<212> DNA
<213> Homo sapiens
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<220>
<221> misc feature
<222> (13)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (83)
<223> n equals a,t,g, or c
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PCT/US00/05881 WO 00/55173

346

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aaaaaaaaa aaaaaaaaa aan
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aaaaaaana
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347

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<221> misc feature
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cgcccccaaa acanataacc aattgtattt atngaaaaat aaatagatac aannnactaa 120
acatagcaat tcagatctnt
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<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> (121)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (122)
<223> n equals a,t,g, or c
<220>
<221> misc feature
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<223> n equals a,t,g, or c
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<221> misc feature
<222> (126)
<223> n equals a,t,g, or c
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<220>

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<222> (150)
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nnncengggg gggncecccc ccccctttn ccccctt
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<211> 358
<212> DNA
<213> Homo sapiens
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<221> misc feature
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gcaagcgcca tatgagcctg gcgncgccaa tagcgaatcc tgttgtgggc ttttttggcct 120
attecegece cteagtettg cegggatgge acegecegea taggaettee agggttggge 180
tgagtgggag ttcgactgct gggnctngta attctcgctt tgggggctgc tccttccagg 240
ctggggacac actggggccc gttgttcggt ctcccgtcct ccgacatctt gtctggaact 300
tncgnctngc agtttccata ggagttggag nctgtgcggc ntaattttgg tggaaaaa
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<211> 399
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<221> misc feature
<222> (70)
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350

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<221> misc feature
<222> (239)
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<222> (316)
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<222> (325)
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<223> n equals a,t,g, or c

WO 00/55173 PCT/US00/05881

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aaaacccaan tcagagtatc canaaatcca agccaggtca aaaccaaaac gaaantntca 120
agcaatccaa atcaagtcaa aaacaaaaac caaagtgccg gtacaggcnt nccgtgggtg 180
atcaggccac ccttccactc aaatggagtg ggnaantncc aaagactagt nttaccaant 240
ttcanatntc cggantccaa gngcctgtnc cttcccagng ttnagccgct gnattgatcc 300
tctgtggggg cctgcnaaac gccantctgg cgaggtgttc cactggggna attgcctacc 360
cggnagtgct ctcaggttct gngtccctca agctggcca
<210> 401
<211> 189
<212> DNA
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<222> (162)
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<220>
<221> misc feature
<222> (165)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (166)
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PCT/US00/05881 WO 00/55173

353

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<222> (187)
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cccccntt
<210> 402
<211> 174
<212> DNA
<213> Homo sapiens
<220>
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<222> (10)
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<222> (73)
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<222> (103)
<223> n equals a,t,g, or c
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<222> (107)
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<220> '
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<223> n equals a,t,g, or c
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<222> (146)
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<223> n equals a,t,g, or c

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<220>
<221> misc feature
<222> (149)
<223> n equals a,t,g, or c
<220>
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<222> (167)
<223> n equals a,t,g, or c
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cctctgacac tcnagcctgg gtgacagagc gagactccgt ctnaggnaag gaaaaaaaaa 120
aaaaaaaan enegggggg geecengtne ceaattggee etatagnggg tegt
<210> 403
<211> 263
<212> DNA
<213> Homo sapiens
<220>
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<222> (5)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (231)
<223> n equals a,t,g, or c
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<221> misc feature
<222> (236)
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<222> (242)
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<221> misc feature
<222> (252)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (260)
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<223> n equals a,t,g, or c

PCT/US00/05881 WO 00/55173

355

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<220>
<221> misc feature
<222> (172)
<223> n equals a,t,g, or c
<220>
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<222> (217)
<223> n equals a,t,g, or c
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<222> (223)
<223> n equals a,t,g, or c
<400> 405
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tgccgaatca actagccctg aaaatggatg gcgctggagc gtcgggccca tacccgtccg 120
tegeeggeag tegagagtgg acggganegg egggggenge gegegegeg gnegtgatgg 180
tgtgcgtcgg agggcggcgg cggcggcggg ggtgtgnggt ccn
<210> 406
<211> 104
<212> DNA
<213> Homo sapiens
<220>
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<222> (8)
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<220>
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<222> (37)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (81)
<223> n equals a,t,g, or c
<220>
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<222> (93)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (103)
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<223> n equals a,t,g, or c

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<400> 406
cccacgente egeogacage ageageetea ccatgangtt getgatggte etcatgetgg 60
                                                                   104
cggccctctc ccagcactgc nacgcaggct ctngctgccc ctna
<210> 407
<211> 66
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (17)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (21)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (57)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (66)
<223> n equals a,t,g, or c
<400> 407
gccctatagt gagtctngta ncaattcact ggccgtcgtt ttacaacgtc gtgacgngga 60
                                                                   66
aaactn
<210> 408
<211> 278
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (6)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (19)
<223> n equals a,t,g, or c
<220>
<221> misc feature
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PCT/US00/05881

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<222> (252)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (275)
<223> n equals a,t,g, or c
<400> 408
gggcanagca ageteetgna ceteaagtga tecacatgee ttggttgace aaattgetgg 60
gattacaggc atgagccaat atgaccagct caaacatctt ctttttaaat gtcagaagca 120
tgtatagtga ttatttctta ttttttcccc cttgatccat ctcaccagat gtttgttgat 180
tttataagaa ttttcaaact accagettet ggetttgttg aacttgggat ttetgtttca 240
ctaattttct tnctcctgtc ttgtacttac tttgntgg
<210> 409
<211> 168
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (16)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (38)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (127)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (140)
<223> n equals a,t,g, or c
<220>
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<222> (143)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (145)
<223> n equals a,t,g, or c
<220>
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<221> misc feature
<222> (167)
<223> n equals a,t,g, or c
<400> 409
aataaaactc taaaangatc actataaaaa aagcaggnac gcctgcaggt accggtccgg 60
aattocoggg togaccoacg cgtocgacgg otgogagaag acgacagaag ggcacggotg 120
cgagaanacg acagaagggn gcnantgaaa gaaggcggca gaaaggnt
<210> 410
<211> 415
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (307)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (347)
<223> n equals a,t,g, or c
<400> 410
tgaataccta agatttctgt cttggggttt ttggtgcatg cagttgatta cttcttattt 60
ttcttaccaa ttgtgaatgt tggtgtgaaa caattaatga agcttttgaa tcatccctat 120
tctgtgtttt atctagtcac ataaatggat taattactaa tttcagttga gaccttctaa 180
ttggttttta ctgaaacatt gagggaacac aaatttatgg gcttcctgat gatgattctt 240
ctaggcatca tgtcctatag tttgtcatcc ctgatgaatg taaaattaca ctgttcacaa 300
aggittingto tootttocac tgctattaat catggtcact ctccccnaaa tattatattt 360
tttctattaa aagaaaaaaa tggaaaaaaa ttacaaggca atggaaacta ttata
<210> 411
<211> 636
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (383)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (512)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (519)
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<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (544)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (547)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (583)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (599)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (603)
<223> n equals a,t,g, or c
<400> 411
gcagatcaga cgtggcgacc cgctgaattt aagcatatta gtcagcggag gagaagaaac 60
taaccaggat tccctcagta acggcgagtg aacagggaag agcccagcgc cgaatccccg 120
ccccqcqqcq qqqcqcgqqa catqtqqcqt acggaagacc cgctccccqg cgccqctcgt 180
ggggggccca agtccttctg atcgaggccc agcccgtgga cggtgtgagg ccggtagcgg 240
ccccqqcqc qccqgqcccq gqtcttcccq gaqtcqqqtt qcttqqqaat qcaqcccaaa 300
gcgggtggta aactccatct aaggctaaat ccccttgtaa atttaactgt tagtccaaag 360
aggaacagct ctttggacac tangaaaaaa ccttgtagag agagtaaaaa atttaacacc 420
catagtaggc ctaaaagcag ccaccaatta agaaagcgtt caagctcaac acccactacc 480
taaaaaaatcc caaacatata actgaactcc tnacacccna ttggaccaat ctatcaccct 540
atanaanaac taatggtagt ataagtaaca tgaaaacatt ctncttcgca taagcctgng 600
                                                                   636
tanattaaaa cacttgaact gaccattaac aggcca
<210> 412
<211> 182
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (129)
<223> n equals a,t,g, or c
<220>
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<221> misc feature
<222> (166)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (169)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (170)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (172)
<223> n equals a,t,g, or c
<400> 412
ccattgattt ttatcaatag tcgtattcat acggatagtc ctggtattgt tccatcacat 60
tctgaggatg ctcttcgaac tcttcaaatt cttcttccat atatcacctt aaatagtgga 120
ttgcggtant aaagattgtg cctgtctttt aaccacatca ggctcngann gntctcgtga 180
                                                                   182
ac
<210> 413
<211> 387
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (157)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (253)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (317)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (323)
<223> n equals a,t,g, or c
<220>
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<221> misc feature
<222> (349)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (351)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (364)
<223> n equals a,t,g, or c
<400> 413
togacccacg cgtccgcca cgcgtccgcc aagaccaccc tcctttcatt tgctagaagg 60
actcactaga ctcaggaaag ctgttaggct cacagttaca gtttattaca gtaaaaggac 120
agagattaag atcagcaaag ggaggaggtg cacagcnacg ttccacgaca gatgaggcga 180
cggcttccat ctgccctctc ccagtggagc catataggca gcacctgatt ctcacagcaa 240
catgtgacaa canccaagaa gtactgccaa tactgccaac cagagcagct tcactcggag 300
atctttgtgt tccaganttt ttngtttgtc ttggagacag ggtctgggnc ngtttgggca 360-
                                                                   387
gacnaagagt acatggtgga gattcac
<210> 414
<211> 276
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (60)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (186)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (195)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (237)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (260)
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<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (266)
<223> n equals a,t,g, or c
<400> 414
gcaaaggtcc atactggtta cttggtttca ttgccaccac ttagtggatg ttcagtttan 60
aaccattttg tetgeteect etggaageet tgegeatage ttaetttgta attgttggag 120
aataactgct gaatttttag ctgttttgag ttgattcgca ccactgcacc acaactcact 180
atgaanacta tttancttat ttattatctt gtgaaaagta taccatgaaa attttgntca 240
tactgtattt atcaagtatn attaanagca ctagat
<210> 415
<211> 192
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (78)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (88)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (99)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (145)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (150)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (164)
<223> n equals a,t,g, or c
<220>
<221> misc feature
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<221> misc feature

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<222> (168)
<223> n equals a,t,g, or c
<400> 415
aaaagattgg actaagacac tggccatacc actggacagg gttatgttaa cacctgaaat 60
tgctgggtct tgagagancc caacgcantt ctgggagang gaccacattg gggggtaggt 120
ccacgggctt ggtgatagaa ttatntctcn atcgacttct tgantgcnat atgaactgta 180
acatttgctt ag
<210> 416
<211> 439
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (7)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (9)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (64)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (406)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (417)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (421)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (431)
<223> n equals a,t,g, or c
<220>
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<222> (434)
<223> n equals a,t,g, or c
<400> 416
gcgagantnc gacagaaggg tacggctgcg agagacgaca gaagggtacg gctgcgagaa 60
gacnacagaa gggtacggct gcgagaagac gacagaaggg tacggctgcg agaagacgac 120
agaagggtac ggctgcgaga agacgacaga aggtacggct gcgagaagac gacagaagga 180
tacggctgcg agaagacgac agaagggaga atcttagttc aactttaaat ttgcccacag 240
aaccctctaa atccccttgt aaatttaact gttagtccaa agaggaacag ctctttggac 300
actaggaaaa aaccttgtag agagagtaaa aaatttaaca cccatagtag gcctaaaaagc 360
agccaccaat taagaaagcg ttcaaagctc aacaccaact acccanaaaa taaaaanaaa 420
naaaaacccg nggnccgct
<210> 417
<211> 155
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (9)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (84)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (122)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (123)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (143)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (153)
<223> n equals a,t,g, or c
<400> 417
gacatettnt tggtttttat tttgaaacaa tttttagget tgttccgggg gtctctgtgc 60
tgcctqtact qtattgacct gttntatagg tgccttttta ttaaaaagaa aattcaaaaa 120
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155
annaaaaaaa aaattaataa aanaaaaaaa aanca
<210> 418
<211> 291
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (285)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (286)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (288)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (289)
<223> n equals a,t,g, or c
<220>
<221> misc feature
<222> (291)
<223> n equals a,t,g, or c
<400> 418
gaaaaaagaa atccatatct taaagaaaca gctttcaagt gcctttctgc agtttttcag 60
gagcgcaaga tagatttgga ataggaataa gctctagttc ttaacaaccg acactcctac 120
aagatttaga aaaaagttta caacataatc tagtttacag aaaaatcttg tgctagaata 180
ctttttaaaa ggtattttga ataccattaa aactgctttt ttttttccag caagtatcca 240
accaacttgg ttctgcttca ataaatcttt ggaaaaacta atttnnanna n
<210> 419
<211> 340
<212> PRT
<213> Homo sapiens
<220>
<221> SITE
<222> (2)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
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	2> (. 3> Xa		qual	s an	y of	the	nati	ural	ly o	ccur	ring	L-ai	nino	acio	ds
)> 4: Xaa		Trp	Phe 5	Leu	Trp	Tyr	Val	Lys 10	Lys	Cys	Gly	Gly	Thr 15	Thr
Arg	Ile	Ile	Ser 20	Thr	Thr	Asn	Gly	Gly 25	Gln	Glu	Arg	Lys	Phe 30	Val	Gly
Gly	Ser	Gly 35	Gln	Val	Ser	Glu	Arg 40	Ile	Met	Asp	Leu	Leu 45	Gly	Asp	Arg
Val	Lys 50	Leu	Glu	Arg	Pro	Val 55	Ile	Tyr	Ile	Asp	Gln 60	Thr	Arg	Glu	Asn
Val 65	Leu	Val	Glu	Thr	Leu 70	Asn	His	Glu	Met	Tyr 75	Glu	Ala	Lys	Tyr	Val 80
Ile	Ser	Ala	Ile	Pro 85	Pro	Thr	Leu	Gly	Met 90	Lys	Ile	His	Phe	Asn 95	Pro
Pro	Leu	Pro	Met 100	Met	Arg	Asn	Gln	Met 105	Ile	Thr	Arg	Val	Pro 110	Leu	Gly
Ser	Val	Ile 115	Lys	Cys	Ile	Val	туг 120	Tyr	Lys	Glu	Pro	Phe 125	Trp	Arg	Lys
Lys	Asp 130	Tyr	Cys	Gly	Thr	Met 135	Ile	Ile	Asp	Gly	Glu 140	Glu	Ala	Pro	Val
Ala 145	Tyr	Thr	Leu	Asp	Asp 150	Thr	Lys	Pro	Glu	Gly 155	Asn	туг	Ala	Ala	11e
Met	Gly	Phe	Ile	Leu 165	Ala	His	Lys	Ala	Arg 170	Lys	Leu	Ala	Arg	Leu 175	Thr
Lys	Glu	Glu	Arg 180	Leu	Lys	Lys	Leu	Cys 185	Glu	Leu	Tyr	Ala	Lys 190	Val	Leu
Gly	Ser	Leu 195	Glu	Ala	Leu	Glu	Pro 200	Val	His	Туr	Glu	Glu 205	Lys	Asn	Trp
Сув	Glu 210	Glu	Gln	туг	Ser	Gly 215	Gly	Cys	Tyr	Thr	Thr 220	туг	Phe	Pro	Pro
Gly 225	Ile	Leu	Thr	Gln	Туг 230	Gly	Arg	Val	Leu	Arg 235	Gln	Pro	Val	Asp	Arg 240
Ile	Tyr	Phe	Ala	Gly 245	Thr	Glu	Thr	Ala	Thr 250	His	Trp	Ser	Gly	Tyr 255	Met

Glu Gly Ala Val Glu Ala Gly Glu Arg Ala Ala Arg Glu Ile Leu His Ala Met Gly Lys Ile Pro Glu Asp Glu Ile Trp Gln Ser Glu Pro Glu Ser Val Asp Val Pro Ala Gln Pro Ile Thr Thr Thr Phe Leu Glu Arg 290 295 His Leu Pro Ser Val Pro Gly Leu Leu Arg Xaa Ile Gly Leu Thr Thr 310 Ile Phe Ser Ala Thr Ala Leu Gly Phe Leu Ala His Lys Arg Gly Leu Leu Val Arg Val 340 <210> 420 <211> 111 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (48) <223> Xaa equals any of the naturally occurring L-amino acids <400> 420 Thr Arg Asp Leu Val Ser Phe Ile Ser Gly Ile Arg Leu Tyr Asn Leu Met Leu Ser Val Leu Arg His Lys Arg Gln Asn Val Ala Tyr Phe Arg 25 20 Ile Cys Phe Phe Ile Glu Val Ser Gly Ile Leu Ser Lys Ile Val Xaa 40 Ser Arg His Cys Ser Leu Cys Ser Ser Gly Thr Ser Cys Pro Leu Leu 55 Ser Leu Gln Ala Thr Gly Asn Ala Ser Val Leu Val Ser Trp Arg Lys 70 Ile Thr Trp Gly Glu Gly Thr Ser Cys Gly Lys Ser Lys Cys Arg Tyr

90

Glu Met Arg Arg Leu Pro Gln Leu Lys Val Asp Lys Ser Ala Leu

369

100 105 110

<210> 421

<211> 61

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (1)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 421

Xaa Ile Trp Cys Ile Ile Cys Lys Glu Ser Lys Met Met Ser Phe Pro 1 5 10 15

Arg Gly Met Asn Leu Arg Asn Ala Phe Asp Gly Asp Val Ser Val Thr 20 25 30

Leu Cys Tyr Ser Gly Ser Ser Asn Asn Ser Lys Ala Asn Tyr Ser Lys 35 40 45

Cys Lys Ile Phe Leu Phe Pro Arg Phe Thr Phe Val Trp 50 55 60

<210> 422

<211> 51

<212> PRT

<213> Homo sapiens

<400> 422

Thr His Ala Tyr Cys Ser Asn Leu Ser Phe Arg Leu Tyr Asp Gln Trp

Arg Ala Trp Met Gln Lys Ser His Lys Thr Arg Asn Gln His Arg Thr
20 25 30

Arg Gly Ser Cys Pro Arg Ala Asp Gly Ala Arg Arg Glu Val Leu Pro 35 40 45

Asp Lys Leu

50

<210> 423

<211> 246

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<212> PRT
<213> Homo sapiens
<220>
<221> SITE
<222> (71)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (101)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (117)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (147)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 423
Thr Arg Asn Asp Met Lys Ala Asp Cys Ile Leu Tyr Tyr Gly Phe Gly
                  5
                                     10
Asp Ile Phe Arg Ile Ser Ser Met Val Val Met Glu Asn Val Gly Gln
             20
                                 25
Gln Lys Leu Tyr Glu Met Val Ser Tyr Cys Gln Asn Ile Ser Lys Cys
                             40
Arg Arg Val Leu Met Ala Gln His Phe Asp Glu Val Trp Asn Ser Glu
    50
                         55
Ala Cys Asn Lys Met Cys Xaa Asn Cys Cys Lys Asp Ser Ala Phe Glu
Arg Lys Asn Ile Thr Glu Tyr Cys Arg Asp Leu Ile Lys Ile Leu Lys
                                     90
Gln Ala Glu Gly Xaa Gly Met Glu Lys Leu Thr Pro Ile Gly Asn Trp
                                105
            100
Ile Asp Ser Trp Xaa Gly Lys Gly Ala Ala Lys Leu Arg Val Ala Gly
                           120
Val Val Ala Pro Thr Leu Pro Arg Glu Asp Leu Glu Lys Ile Ile Ala
    130
                      135
```

371

His Phe Xaa Ile Gln Gln Tyr Leu Lys Glu Asp Tyr Ser Phe Thr Ala 150 155 145 Tyr Ala Thr Ile Ser Tyr Leu Lys Ile Gly Pro Lys Ala Asn Leu Leu 165 170 Asn Asn Glu Ala His Ala Ile Thr Met Gln Val Thr Lys Ser Thr Gln 185 180 Asn Ser Phe Arg Ala Glu Ser Ser Gln Thr Cys His Ser Glu Gln Gly 200 Asp Lys Lys Met Glu Glu Lys Asn Ser Gly Asn Phe Gln Lys Lys Ala 215 Ala Asn Met Leu Gln Gln Ser Gly Ser Lys Asn Thr Gly Ala Lys Lys 230 235 Arg Lys Ile Asp Asp Ala 245 <210> 424 <211> 109 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (77) <223> Xaa equals any of the naturally occurring L-amino acids Asp His Trp Pro Arg Pro Glu Trp Leu Pro Cys Thr Ser Trp Arg Arg Ala Ser Cys Leu Asn His Val Asn Cys His His Leu Ala Thr Pro Ala 25 Pro Ala Ser Ala Leu Pro Pro Phe Pro Pro Ser Trp Ser Gly Gly Tyr 35 40 Arg Ser Leu Gly Pro Thr Leu Ala Pro Leu Ser Pro Ala Ser Val Cys Leu Thr Val Phe Pro Pro Leu Pro Gln Leu Arg Cys Xaa Pro Gln Ala 65 Trp Cys Cys Leu Gly Gly Leu Gly Glu Gly Val Cys Gly Gly Arg

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Arg Val Lys Thr Glu Ala Arg Cys Gln Asn Gly Leu Glu
100 105
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<210> 425

<211> 57

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (5)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (49)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 425

Gly Ser Glu Thr Xaa Lys Tyr Leu Val Glu Asp Lys Arg Leu Gly Leu 1 5 10 15

Tyr Thr Trp Leu Cys Thr Asp Leu Leu Ser His Ile Gly Asn His His
20 25 30

Thr Leu Gln Gly Ile Ser Phe Ile Cys Lys Met Gln Arg Leu Val Leu 35 40 45

Xaa Asn His Thr Asn Phe Phe Val Leu 50 55

<210> 426

<211> 99

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (96)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 426

Phe Gly Thr Ser Gly Asp Gly Gly Gly Ser Lys Met Ala Gln Ala Ile
1 10 15

Phe Glu Ala Leu Glu Gly Met Asp Asn Gln Thr Val Leu Ala Val Gln

20 25 30

Ser Leu Leu Asp Gly Gln Gly Ala Val Pro Asp Pro Thr Gly Gln Ser 35 40 45

Val Asn Ala Pro Pro Ala Ile Gln Pro Leu Asp Asp Glu Asp Val Phe 50 60

Leu Cys Gly Lys Cys Lys Lys Gln Phe Asn Ser Leu Pro Ala Phe Met 65 70 75 80

Thr His Lys Arg Glu Gln Cys Gln Gly Asn Ala Pro Ala Leu Ala Xaa 90 95

Val Ser Leu

<210> 427

<211> 55

<212> PRT

<213> Homo sapiens

<400> 427

Asn Ser Asn Ser Ser Ile Phe Ser Leu Val Ser Val Lys Cys Asp Lys

1 5 10 15

Ser Thr Tyr Phe Lys Leu Phe Ser Ala Leu Gly Tyr Ser Ser Asn Lys 20 25 30

Asn Thr Asn Leu Trp Val Phe Lys Lys Thr Trp Arg Ile Asn Ser Tyr 35 40 45

Phe Lys Arg Ser Lys Lys Lys 50 55

<210> 428

<211> 54

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (41)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 428

His Thr Leu Ser Asn Leu Glu Phe Ala Gln Lys Val Glu Pro Cys Asn

374

15 1 5 10 Asp His Val Arg Ala Lys Leu Ser Trp Ala Lys Lys Arg Asp Glu Asp 25 Asp Val Pro Thr Val Pro Ser Thr Xaa Gly Glu Glu Arg Leu Tyr Asn 40 Pro Phe Leu Arg Val Ala 50 <210> 429 <211> 39 <212> PRT <213> Homo sapiens <400> 429 Arg Gln Thr Lys Val Asn Leu Lys Glu Thr Arg Ser Phe Glu Ile Ile Val Trp Gly Phe Tyr Lys Ser Asn Tyr Cys His Leu His Pro Asp Ser 20 25 Phe Lys Leu Leu Ile His Pro 35 <210> 430 <211> 133 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (81) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (85) <223> Xaa equals any of the naturally occurring L-amino acids <400> 430 Ala Arg Ala Pro Arg Val Pro Pro Ala Pro His Thr Pro Ser Lys Met 5 10 Gly Lys Glu Lys Thr His Ile Asn Ile Val Val Ile Gly His Val Asp

. 25

Ser Gly Lys Ser Thr Thr Thr Gly His Leu Ile Tyr Lys Cys Gly Gly
35 40 45

Ile Asp Lys Arg Thr Ile Glu Lys Phe Glu Lys Glu Ala Ala Glu Met 50 55 60

Gly Lys Gly Ser Phe Lys Tyr Ala Trp Val Leu Asp Lys Leu Lys Ala 65 70 75 80

Xaa Val Ser Ala Xaa Ile Thr Ile Asp Ile Ser Leu Trp Lys Phe Glu 85 90 95

Thr Thr Lys Tyr Tyr Ile Thr Ile Ile Asp Ala Pro Gly His Arg Asp 100 105 110

Phe Ile Lys Asn Met Ile Thr Gly Thr Ser Gln Ala Asp Cys Ala Val 115 120 125

Leu Ile Val Ala Ala 130

<210> 431

<211> 190

<212> PRT

<213> Homo sapiens

<400> 431

Leu Cys Trp Ala Arg Pro Leu Pro Ser Gly Pro Val Leu Leu Ala Ala 1 5 10 15

Asn Lys Asp Ser Ser Trp Cys Pro Thr Cys Leu Val His Cys Cys Val 20 25 30

Asn Pro Gly Gly Ser Gly His Arg Arg Gln Pro Arg Pro Arg Val Gln 35 40 45

Glu Lys Cys Ser Leu Glu Ala Arg Thr Thr Ala Ser His Trp Gly Arg
50 55 60

Arg Gly Pro Arg Thr Thr Ser Ala Ser Tyr Leu Pro Ala Ser Ala Arg
65 70 75 80

Gly Pro Arg Asp Ala Val Leu Phe Gln Pro Pro Ala Leu Gly Arg Gly
85 90 95

His Ala Ser Arg Ile Gln Gly Ala Gly Gly Leu Ser Thr Ala Arg Thr 100 105 110

376

Cys Leu Leu Ala Ala Ala Val Gly Glu His Gly Gly Cys Gln Arg

Leu Leu Trp Lys Val Ala Ala Ser Glu Met Ala Gly Ala Ala Gly Val 130 135 140

Arg Leu His Thr Ala Gln Val Ser Ser Gly Arg Leu Ser Trp Gly Gly
145 150 155 160

Ser Ser Ser Ala Glu Gly Trp Trp Gly Val Gln Ser Val Ile Leu Gly
165 170 175

Ala Val Cys Pro Thr Pro Ala Trp Gly Pro His Phe Arg Arg 180 185 190

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<211> 310

<212> PRT

<213> Homo sapiens

<400> 432

Gly Pro His Gly Asn Gly Glu Val Arg Trp Pro Leu Pro Pro Pro 1 5 10 15

Pro Arg Phe Val Ala Arg Arg Lys Met Ala Asp Leu Glu Glu Gln Leu 20 25 30

Ser Asp Glu Glu Lys Val Arg Ile Ala Ala Lys Phe Ile Ile His Ala 35 40 45

Pro Pro Gly Glu Phe Asn Glu Val Phe Asn Asp Val Arg Leu Leu 50 55 60

Asn Asn Asp Asn Leu Leu Arg Glu Gly Ala Ala His Ala Phe Ala Gln 65 70 75 80

Tyr Asn Leu Asp Gln Phe Thr Pro Val Lys Ile Glu Gly Tyr Glu Asp
85 90 95

Gln Val Leu Ile Thr Glu His Gly Asp Leu Gly Asn Gly Lys Phe Leu 100 105 110

Asp Pro Lys Asn Arg Ile Cys Phe Lys Phe Asp His Leu Arg Lys Glu

Ala Thr Asp Pro Arg Pro Cys Glu Val Glu Asn Ala Val Glu Ser Trp 130 135 140

Arg Thr Ser Val Glu Thr Ala Leu Arg Ala Tyr Val Lys Glu His Tyr

160 150 155 145 Pro Asn Gly Val Cys Thr Val Tyr Gly Lys Lys Ile Asp Gly Gln Gln 170 165 Thr Ile Ile Ala Cys Ile Glu Ser His Gln Phe Gln Ala Lys Asn Phe 180 185 Trp Asn Gly Arg Trp Arg Ser Glu Trp Lys Phe Thr Ile Thr Pro Ser 200 Thr Thr Gln Val Val Gly Ile Leu Lys Ile Gln Val His Tyr Tyr Glu 210 215 Asp Gly Asn Val Gln Leu Val Ser His Lys Asp Ile Gln Asp Ser Leu 235 Thr Val Ser Asn Glu Val Gln Thr Ala Lys Glu Phe Ile Lys Ile Val 250 245 Glu Ala Ala Glu Asn Glu Tyr Gln Thr Ala Ile Ser Glu Asn Tyr Gln 260 265 Thr Met Ser Asp Thr Thr Phe Lys Ala Leu Arg Arg Gln Leu Pro Val 280 Thr Arg Thr Lys Ile Asp Trp Asn Lys Ile Leu Ser Tyr Lys Ile Gly 295 Lys Glu Met Gln Asn Ala 305 310 <210> 433 <211> 289 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (287) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (288) <223> Xaa equals any of the naturally occurring L-amino acids <400> 433

Gln Ser Cys Thr Ser Gly Ser Ser Lys Pro Asn Ser Pro Ser Ile Ser

PCT/US00/05881

378

WO 00/55173

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Pro	Ser	Ile	Leu 20	Ser	Asn	Thr	Glu	His 25	Lys	Arg	Gly	Pro	Glu 30	Val	Thr
Ser	Gln	Gly 35	Val	Gln	Thr	Ser	Ser 40	Pro	Ala	Cys	Lys	Gln 45	Glu	Lys	Asp
Asp	Lys 50	Glu	Glu	Lys	Lys	Asp 55	Ala	Ala	Glu	Gln	Val 60	Arg	Lys	Ser	Thr
Leu 65	Asn	Pro	Asn	Ala	Lys 70	Glu	Phe	Asn	Pro	Arg 75	Ser	Phe	Ser	Gln	Pro 80
Lys	Pro	Ser	Thr	Thr 85	Pro	Thr	Ser	Pro	Arg 90	Pro	Gln	Ala	Gln	Pro 95	Ser
Pro	Ser	Met	Val 100	Gly	His	Gln	Gln	Pro 105	Thr	Pro	Val	Tyr	Thr 110	Gln	Pro
Val	Суз	Phe 115	Ala	Pro	Asn	Met	Met 120	Tyr	Pro	Val	Pro	Val 125	Ser	Pro	Gly
Val	Gln 130	Pro	Leu	Туг	Pro	Ile 135	Pro	Met	Thr	Pro	Met 140	Pro	Val	Asn	Gln
Ala 145	Lys	Thr	туг	Arg	Ala 150	Gly	Lys	Val	Pro	Asn 155	Met	Pro	Gln	Gln	Arg 160
Gln	Asp	Gln	His	His 165	Gln	Ser	Ala	Met	Met 170	His	Pro	Ala	Ser	Ala 175	Ala
Gly	Pro	Pro	Ile 180	Ala	Ala	Thr	Pro	Pro 185	Ala	Tyr	Ser	Thr	Gln 190	Tyr	Val
Ala	Tyr	Ser 195	Pro	Gln	Gln	Phe	Pro 200	Asn	Gln	Pro	Leu	Val 205	Gln	His	Val
Pro	His 210	Tyr	Gln	Ser	Gln	His 215	Pro	His	Val	Tyr	Ser 220	Pro	Val	Ile	Gln
Gly 225	Asn	Ala	Arg	Met	Met 230	Ala	Pro	Pro	Thr	His 235	Ala	Gln	Pro	Gly	Leu 240
Val	Ser	Ser	Ser	Ala 245	Thr	Gln	Tyr	Gly	Ala 250	His	Glu	Gln	Thr	His 255	Ala
Met	Tyr	Ala	Cys 260	Pro	Lys	Leu	Pro	Туг 265	Asn	Lys	Glu	Thr	Ser 270	Pro	Ser
Phe	Tyr	Phe	Ala	Ile	Ser	Thr	Gly	Ser	Leu	Ala	Gln	Gln	Tyr	Xaa	Xaa

379

275 280 285

Pro

<210> 434

<211> 147

<212> PRT

<213> Homo sapiens

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Lys Val Thr Pro Asp Leu Lys Pro Thr Glu Ala Ser Ser Ala Phe
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Arg Leu Met Pro Ala Leu Gly Val Ser Val Ala Asp Gln Lys Gly Lys
20 25 30

Ser Thr Val Ala Ser Ser Glu Ala Lys Pro Ala Ala Thr Ile Arg Ile 35 40 45

Val Gln Gly Leu Gly Val Met Pro Pro Lys Ala Gly Gln Thr Ile Thr
50 60

Val Ala Thr His Ala Lys Gln Gly Ala Ser Val Ala Ser Gly Ser Gly 65 70 75 80

Thr Val His Thr Ser Ala Val Ser Leu Pro Ser Met Asn Ala Ala Val 85 90 95

Ser Lys Thr Val Ala Val Ala Ser Gly Ala Ala Arg Pro Pro Ser Ala 100 105 110

Ser Ala Gln Glu Pro Pro Pro Cys Gly Arg Ser Leu Ser Ala Pro Arg 115 120 125

Leu Cys Pro Arg Pro Arg Leu Gly Ser Cys Leu His Gly Ser Gln Phe 130 135 140

Pro Ser Leu

145

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<211> 151

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<213> Homo sapiens

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			•		-				•		_				
<22	0>														
	1> S	TTE													
	2> (
	•	,	ובוים	s an	v of	+he	nati	ural	1 1 1	cour	rina	Ta:	nino	acio	de
-22	J- 1.	uu c	guur.	J 411.	, 01	CIIC		u _u_	-, 0						
-40	0> 4:	26													
				Dro	17-1	Mot	Dro	Dra	C1 n	mh ∽	Cl n	car	Dro	C1v	Gl n
	PLO	Ala	ser	Pro	vaı	Mec	PIO	PLO	10	THE	GIII	ser	PIU	15	GIII
1				5					10					13	
_			_				•••			•• / -	~1 -	.	a1 -	C	3
Pro	Ala	GIN		Ala	Pro	met	val		ren	HIS	GIN	rås		ser	Arg
			20					25					30		
					_	_	_			_	_				
He	Thr		He	Gln	Lys	Pro	_	GIA	xaa	Asp	Pro		GIU	тте	Leu
		35					40					45			
Gln	Glu	Arg	Glu	Tyr	Arg	Leu	Gln	Ala	Arg	Ile		His	Arg	Ile	Gln
	50					55					60				
Glu	Leu	Glu	Asn	Leu	Pro	Gly	Ser	Leu	Ala	Gly	Asp	Leu	Arg	Thr	Lys
65					70					75					80
Ala	Thr	Ile	Glu	Leu	Lys	Ala	Leu	Arg	Leu	Leu	Asn	Phe	Gln		Gln
				85					90					95	
Leu	Arg	Gln	Glu	Val	Val	Val	Cys	Met	Arg	Arg	Asp	Thr	Ala	Leu	Glu
			100					105					110		
Thr	Ala	Leu	Asn	Ala	Lys	Ala	Tyr	Lys	Arg	Xaa	Ser	Ala	Ser	Pro	Cys
		115					120					125			
Ala	Arg	Pro	Ala	Ser	Leu	Arg	Ser	Trp	Arg	Ser	Ser	Arg	Arg	Ser	Ser
	130					135					140				
Ara	Ser	Ala	Ser	Ala	Glv	Ara	Ser	Thr	Ara	Asn	Thr	Ser	Ile	Ala	Phe
145					150	5			5	155					160
- • •															
Ser	Ser	Met	Pro	Arg	Tle	Ser	Ara	Acn	Tle	ጥb r	Asp	Pro	Ser	G] n	Ala
JGL	551		0	165	110	JUL	*** 9	.1311	170	1111				175	
				100					1/0					- / 3	
Tuc	Ser	A = ~	Sar												
пåя	Set	urd	Ser												

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Arg Lys Tyr Leu Val Pro Leu Xaa Lys Lys Leu Tyr Leu Lys Trp Ala
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Leu Glu Glu Tyr Leu Asp Glu Phe Asp Pro Cys His Cys Arg Pro Cys
                                 25
Gln Asn Gly Gly Leu Ala Thr Val Glu Gly Thr His Cys Leu Cys His
         35
Cys Lys Pro Tyr Thr Phe Gly Ala Ala Cys Glu Gln Gly Val Leu Val
Gly Asn Gln Ala Gly Gly Val Asp Gly Gly Trp Ser Cys Trp Ser Ser
                     70
                                         75
Trp Ser Pro Cys Val Gln Gly Lys Lys Thr Arg Ser Arg Xaa Cys Xaa
                 85
                                     90
Asn Pro Pro Pro Ser Gly Gly Gly Arg Ser Cys Val Gly Glu Thr Thr
                                105
Glu Ser Thr Gln Cys Glu Asp Glu Glu Leu Glu His Leu Arg Leu Leu
        115
                            120
Glu Pro His Cys Phe Pro Leu Ser Leu Val Pro Thr Glu Phe Cys Pro
    130
                        135
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Ser 145	Pro	Pro	Ala	Leu	Lys 150	Asp	Gly	Phe	Val	Gln 155	Asp	Glu	Gly	Thr	Met 160
Phe	Pro	Val	Gly	Lys 165	Asn	Val	Val		Xaa 170	Cys	Asn	Glu	Gly	Tyr 175	Ser
Leu	Ile	Gly	Asn 180	Pro	Val	Ala	Arg	Cys 185	Gly	Glu	Asp	Leu	Arg 190	Trp	Leu
Val	Gly	Glu 195	Met	His	Cys	Gln	Lys 200	Ile	Ala	Cys	Val	Leu 205	Pro	Val	Leu
Met	Asp 210	Gly	Ile	Gln	Ser	His 215	Pro	Gln	Lys	Pro	Phe 220	Tyr	Thr	Val	Gly
Glu 225	Lys	Val	Thr	Val	Ser 230	Cys	Ser	Gly	Gly	Met 235	Ser	Leu	Glu	Gly	Pro 240
Ser	Ala	Phe	Leu	Cys 245	Gly	Ser	Ser	Leu	Lys 250	Trp	Ser	Pro	Glu	Met 255	Lys
			260					265					270	Val	
_	_	275		_		-	280					285		Cys	
	290					295					300			Asp	
305		-			310					315				Val	320
	-			325		_			330					Cys 335	
			340					345					350	Trp	
		355					360					365		Ser	
	370					375					380			Lys	
385					390					395				Gly	Gln 400
Ser	Ile	Ser	Val	Thr	Ser	Ile	Arg	Pro	Cys	Ala	Ala	Glu	Thr	Gln 415	

PCT/US00/05881

384

WO 00/55173

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Leu Ile Arg Leu Thr Ile Gly Lys Ala Gly Ser Leu Gln Tyr Arg Xaa
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Xaa Xaa Phe Pro Gly Met Glu Ala Phe Leu Gly Ser Arg Ser Gly Leu
Trp Ala Gly Gly Pro Ala Pro Gly Gln Phe Tyr Arg Ile Pro Ser Thr
Pro Asp Ser Phe Met Asp Pro Ala Ser Ala Leu Tyr Arg Gly Pro Ile
                         55
Thr Arg Thr Gln Asn Pro Met Val Thr Gly Thr Ser Val Leu Gly Val
Lys Phe Glu Gly Gly Val Val Ile Ala Ala Asp Met Leu Gly Ser Tyr
Gly Ser Leu Ala Arg Phe Arg Asn Ile Ser Arg Ile Met Arg Val Asn
            100
Asn Ser Thr Met Leu Gly Ala Ser Gly Asp Tyr Ala Asp Phe Gln Tyr
                            120
Leu Lys Gln Val Leu Gly Gln Met Val Ile Asp Glu Glu Leu Leu Gly
                        135
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Asp 145	Gly	His	Ser	Tyr	Ser 150	Pro	Arg	Ala	Ile	His 155	Ser	Trp	Leu	Thr	160
Ala	Met	Tyr	Ser	Arg 165	Arg	Ser	Lys	Met	Asn 170	Pro	Leu	Trp	Asn	Thr 175	Me
Val	Ile	Gly	Gly 180		Ala	Asp	Gly	Glu 185	Ser	Phe	Leu	Gly	Туг 190	Val	Ası
Met	Leu	Gly 195	Val	Ala	Tyr	Glu	Ala 200	Pro	Ser	Leu	Ala	Thr 205	Gly	Tyr	Gly
Ala	Tyr 210	Leu	Ala	Gln	Pro	Leu 215	Leu	Arg	Glu	Val	Leu 220	Glu	Lys	Gln	Pro
Val 225	Leu	Ser	Gln	Thr	Glu 230	Ala	Arg	Asp	Leu	Val 235	Glu	Arg	Cys	Met	Arg 240
Val	Leu	Tyr	Tyr	Arg 245	Asp	Ala	Arg	Ser	Tyr 250	Asn	Arg	Phe	Gln	Ile 255	Ala
Thr	Val	Thr	Glu 260	Lys	Gly	Val	Glu	11e 265	Glu	Gly	Pro	Leu	Ser 270	Thr	Glı
Thr	Asn	Trp 275	Asp	Ile	Ala	His	Met 280	Ile	Ser	Gly	Phe	Glu 285			
<211 <212	0> 43 l> 18 2> PF 3> Ho	35 RT	sapie	ens		-				·					
<400)> 43	19													
			Ala	His 5	Lys	Lys	Gly	Lys	Leu 10	Pro	Ile	Val	Asn	Glu 15	Asp
Asp	Glu		Val 20	Ala	Ile	Ile		Arg 25		Asp	Leu	Lys	Lys 30	Asn	Arg
Asp	Tyr	Pro 35	Leu	Ala	Ser	Lys	Asp 40	Ala	Lys	Lys	Gln	Leu 45	Leu	Суз	Gly
Ala	Ala 50	Ile	Gly	Thr	His	Glu 55	Asp	Asp	Lys	Tyr	Arg 60	Leu	Asp	Leu	Let
Ala 65	Gln	Ala	Gly	Val	Asp 70	Val	Val	Val	Leu	Asp 75	Ser	Ser	Gln	Gly	Asr 80
Ser	Ile	Phe	Gln	Ile	Asn	Met	Ile	Lvs	Tvr	Ile	Lvs	Asp	Lvs	Tvr	Pro

95 85 90 Asn Leu Gln Val Ile Gly Gly Asn Val Val Thr Ala Ala Gln Ala Lys 105 Asn Leu Ile Asp Ala Gly Val Asp Ala Leu Arg Val Gly Met Gly Ser 120 115 Gly Ser Ile Cys Ile Thr Gln Glu Val Leu Ala Cys Gly Arg Pro Gln 135 Ala Thr Ala Val Tyr Lys Val Ser Glu Tyr Ala Arg Arg Phe Gly Val 145 150 155 Pro Val Ile Ala Asp Gly Gly Ile Gln Asn Val Gly His Ile Ala Lys 170 Ala Leu Ala Leu Gly Ala Pro Gln Ser 180 <210> 440 <211> 211 <212> PRT <213> Homo sapiens <400> 440 Leu Gln Gly Arg Ser Thr Pro Ile Trp Pro Ala Leu Ala Thr Val Thr Ser Arg Thr Pro Ala Leu Gly Pro Gln Ala Gly Ile Asp Thr Asn Glu Ile Ala Pro Leu Glu Pro Asp Ala Pro Pro Asp Ala Cys Glu Ala Ser Phe Asp Ala Val Ser Thr Ile Arg Gly Glu Leu Phe Phe Lys Ala 55 Gly Phe Val Trp Arg Leu Arg Gly Gly Gln Leu Gln Pro Gly Tyr Pro 65 70 Ala Leu Ala Ser Arg His Trp Gln Gly Leu Pro Ser Pro Val Asp Ala 90 Ala Phe Glu Asp Ala Gln Gly His Ile Trp Phe Phe Gln Gly Ala Gln 100 105 Tyr Trp Val Tyr Asp Gly Glu Lys Pro Val Leu Gly Pro Ala Pro Leu

120

387

Thr Glu Leu Gly Leu Val Arg Phe Pro Val His Ala Ala Leu Val Trp 135 Gly Pro Glu Lys Asn Lys Ile Tyr Phe Phe Arg Gly Arg Asp Tyr Trp 150 155 Arg Phe His Pro Ser Thr Arg Arg Val Asp Ser Pro Val Pro Arg Arg 165 170 Pro Leu Thr Gly Glu Gly Cys Pro Leu Arg Ser Thr Leu Pro Ser Arg 185 Met Leu Met Ala Met Pro Thr Ser Cys Ala Ala Ala Ser Thr Gly Ser 200 Leu Thr Leu 210 <210> 441 <211> 80 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (40) <223> Xaa equals any of the naturally occurring L-amino acids <400> 441 Gly Gly Ala Gly Lys Leu Leu Ser Phe Thr His Ser Ala Pro Trp Ser Arg Leu Trp Ser Ser Leu Gly Lys Arg Val Thr Gly Glu Ser Gln Gly 20 25 Leu Glu Lys Leu Pro Gly Thr Xaa Asp Gly Leu Ala Ala Leu Thr Gln 40 . Asp Pro Leu Pro Leu Pro Pro Pro Leu Cys Arg Asn Thr Gly Thr Pro

Arg Gly Lys Met Ser Phe Ser Arg Leu Gln Phe Ser Pro Arg Lys Leu

75

388

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Asn Val His Leu Tyr Ile Met Tyr Tyr Met Glu Ala Lys His Ala Val
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Ser Phe Met Thr Cys Thr Gln Asn Val Ala Pro Asp Met Phe Arg Thr

PCT/US00/05881

			20					25					30		
Ile	Pro	Pro 35	Glu	Ala	Asn	Ile	Pro 40	Ile	Pro	Val	Lys	Ser 45	Asp	Met	Val
Met	Met 50	His	Glu	His	His	Lys 55	Glu	Thr	Glu	Tyr	Lys 60	Asp	Lys	Ile	Pro
Leu 65	Leu	Gln	Gln	Pro	Lys 70	Arg	Glu	Glu	Glu	Glu 75	Val	Leu	Asp	Gln	Gly 80
Asp	Phe	туг	Ser	Leu 85	Leu	Ser	Lys	Leu	Leu 90	Gly	Glu	Arg	Glu	Asp 95	Val
Val	His	Val	His 100	Lys	Tyr	Asn	Pro	Thr 105	Glu	Lys	Ala	Glu	Ser 110	Glu	Ser
Asp	Leu	Val 115	Ala	Glu	Ile	Ala	Asn 120	Val	Val	Gln	Lys	Lys 125	Asp	Leu	Gly
Arg	Ser 130	Asp	Ala	Arg	Glu	Gly 135	Ala	Glu	His	Glu	Arg 140	Gly	Asn	Ala	Ile
Leu 145	Val	Arg	Asp	Arg	Ile 150	His	Lys	Phe	His	Arg 155	Leu	Val	Ser	Thr	Leu 160
Arg	Pro	Pro	Glu	Ser 165	Arg	Val	Phe	Ser	Leu 170	Gln	Gln	Pro	Pro	Pro 175	Gly
G1u	Gly	Thr	Trp 180	Glu	Pro	Glu	His	Thr 185	Gly	Asp	Phe	His	Met 190	Glu	Glu
		195		•			Tyr 200					205			
Val	Ala 210	Leu	Xaa	Pro	Lys	Asn 215	Asn	Leu	Val	Ile	Phe 220	His	Arg	Gly	Asp
225			_		230		Phe			235					240
				245			Glu		250					255	
			260				Ser	265					270		
		275					Lys 280					285			
Val	Ala	Leu	His	Gln	Val	Phe	Lvs	Leu	Asp	Pro	Asn	Asn	Lys	Glu	Gly

	290					295					300				
Pro 305	Val	Leu	Ile	Leu	Gly 310	Arg	Ser	Met	Gln	Pro 315	Gly	Ser	Asp	Gln	Asn 320
His	Phe	Cys	Gln	Pro 325	Thr	Asp	Val	Ala	Val 330	Asp	Pro	Gly	Thr	Gly 335	Ala
Ile	Tyr	Val	Ser 340	Asp	Gly	Tyr	Cys	Asn 345	Ser	Arg	Ile	Val	Gln 350	Phe	Ser
Pro	Ser	Gly 355	Lys	Phe	Ile	Thr	Gln 360	Trp	Gly	Glu	Glu	Ser 365	Ser	Gly	Ser
Ser	Pro 370	Leu	Pro	Gly	Gln	Phe 375	Thr	Val	Pro	His	Ser 380	Leu	Ala	Leu	Val
Pro 385	Leu	Leu	Gly	Gln	Leu 390	Cys	Val	Ala	Asp	Arg 395	Glu	Asn	Gly	Arg	Ile 400
Gln	Cys	Phe	Lys	Thr 405	Asp	Thr	Lys	Glu	Phe 410	Val	Arg	Glu	Ile	Lys 415	His
Ser	Ser	Phe	Gly 420	Arg	Asn	Val	Phe	Ala 425	Ile	Ser	Tyr	Ile	Pro 430	Gly	Leu
Leu	Phe	Ala 435	Val	Asn	Gly	Lys	Pro 440	His	Phe	Gly	Asp	Gln 445	Glu	Pro	Val
Gln	Gly 450	Phe	Val	Met	Asn	Phe 455	Ser	Asn	Gly	Glu	11e 460	Ile	Asp	Ile	Phe
Lys 465	Pro	Val	Arg	Xaa	Leu 470	Leu	Asp	Met	Pro	His 475	Asp	Ile	Val	Ala	Ser 480
Glu	Asp	Gly	Thr	Val 485	Tyr	Ile	Gly	Arg	Cys 490	Ser	Tyr	Gln	His	Arg 495	Val
Gly	Ser		Thr 500	Leu	Asp	Xaa		Xaa 505		Gly	Thr	Ser	Val 510	Gln	Phe
Lys	Lys	Gly 515	Leu	Xaa	Ile	Glu	Val 520	Gln	Gly	Asn	Pro	Lys 525	Lys	Pro	Glu
Gly	.Ile 530	Cys	Суз	Phe	Pro	Xaa 535	Thr	Thr	Leu	Arg	Val 540	Ile	Pro	Val	Val
Gly 545	Xaa	Trp	Arg	Gly	His 550	Gly	Pro	Asn	Leu	Ile 555	Pro	Val	Gly	Lys	Asn 560
Pro	Ara	Glv	Pro	Leu	Glv	Ara									

391

565

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 Arg Pro Ser Cys Ser Pro Gly Ser Val Ser Ala Ala Ala Val Asn Met
 Glu Pro Pro Asp Ala Pro Ala Gln Ala Arg Gly Ala Pro Arg Leu Leu
 Leu Leu Ala Val Leu Leu Ala Ala His Pro Asp Ala Gln Ala Glu Val
 Arg Leu Ser Val Pro Pro Leu Val Glu Val Met Arg Gly Lys Ser Val
 Ile Leu Asp Cys Thr Pro Thr Gly Thr His Asp His Tyr Met Leu Glu
                      70
 Trp Phe Leu Thr Asp Arg Ser Gly Ala Arg Pro Arg Leu Ala Ser Ala
                  85
                                      90
 Glu Met Gln Gly Ser Glu Leu Gln Val Thr Met His Asp Thr Arg Gly
                                 105
 Arg Ser Pro Pro Tyr Gln Leu Gly Leu Pro Xaa Gly Ala Trp Xaa Leu
                             120
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Xaa

392

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Leu Asp Arg Lys Asp Lys Phe Ser Phe Asp Leu Gly Lys Gly Glu Val

Ile Lys Ala Trp Asp Ile Ala Ile Ala Thr Met Lys Val Gly Glu Val

		35					40					45			
Cys	His 50	Ile	Thr	Cys	Lys	Pro 55	Glu	Tyr	Ala	Tyr	Gly 60	Ser	Ala	Gly	Ser
Pro 65	Pro	Lys	Ile	Pro	Pro 70	Asn	Ala	Thr	Leu	Val 75	Phe	Glu	Val	Glu	Leu 80
Phe	Glu	Phe	Lys	Gly 85	Glu	Asp	Leu	Thr	Glu 90	Glu	Glu	Asp	Gly	Gly 95	Ile
Ile	Arg	Arg	Ile 100	Gln	Thr	Arg	Gly	Glu 105	Gly	Tyr	Ala	Lys	Pro 110	Asn	Glu
Gly	Ala	11e 115	Val	Glu	Val	Ala	Leu 120	Glu	Gly	Tyr	Tyr	Lys 125	Asp	Lys	Leu
Phe	Asp 130	Gln	Arg	Glu	Leu	Arg 135	Phe	Glu	Ile	Gly	Glu 140	Gly	Glu	Asn	Leu
Asp 145	Leu	Pro	туг	Gly	Leu 150	Glu	Arg	Ala	Ile	Gln 155	Arg	Met	Glu	Lys	Gly 160
Glu	His	Ser	Ile	Val 165	Tyr	Leu	Lys	Pro	Ser 170	Tyr	Ala	Phe	Gly	Ser 175	Val
Gly	Lys	Glu	Lys 180	Phe	Gln	Ile	Pro	Pro 185	Asn	Ala	Glu	Leu	Lys 190	Tyr	Glu
Leu	His	Leu 195	Lys	Ser	Phe	Glu	Lys 200	Ala	Lys	Glu	Ser	Trp 205	Glu	Met	Asn
Ser	Glu 210	Glu	Lys	Leu	Glu	Gln 215	Ser	Thr	Ile	Val	Lys 220	Glu	Arg	Gly	Thr
Val 225	Туг	Phe	Lys	Glu	Gly 230	Lys	Tyr	Lys	Gln	Ala 235	Leu	Leu	Gln	Tyr	Lys 240
Lys	Ile	Val	Ser	Trp 245	Leu	Glu	туr	Glu	Ser 250	Ser	Phe	Ser	Asn	Glu 255	Glu
Ala	Gln	Lys	Ala 260	Gln	Ala	Leu	Arg	Leu 265	Ala	Ser	His	Leu	Asn 270	Leu	Ala
Met	Суз	His 275	Leu	Lys	Leu	Gln	Ala 280	Phe	Ser	Ala	Ala	11e 285	Glu	Ser	Cys
Asn	Lys 290	Ala	Leu	Glu	Leu	Asp 295	Ser	Asn	Asn	Glu	Lys 300	Gly	Leu	Phe	Arg
Arg	Gly	Glu	Ala	His	Leu	Ala	Val	Asn	Asp	Phe	Glu	Leu	Ala	Arg	Ala

320 305 310 315 Asp Phe Gln Lys Val Leu Gln Leu Tyr Pro Asn Asn Lys Ala Ala Lys 330 Thr Gln Leu Ala Val Cys Gln Gln Arg Ile Arg Arg Gln Leu Ala Arg 345 Glu Lys Lys Leu Tyr Ala Asn Met Phe Glu Arg Leu Ala Glu Glu Glu 360 Asn Lys Ala Lys Ala Glu Ala Ser Ser Gly Asp His Pro Thr Asp Thr 370 375 Glu Met Lys Glu Glu Gln Lys Ser Asn Thr Ala Gly Ser Gln Ser Gln 395 Val Glu Thr Glu Ala 405 <210> 446 <211> 232 <212> PRT <213> Homo sapiens <400> 446 Pro Leu Val Pro Ser Ser Gln Lys Ala Leu Leu Leu Glu Leu Lys Gly Leu Gln Glu Glu Pro Val Glu Gly Phe Arg Val Thr Leu Val Asp Glu Gly Asp Leu Tyr Asn Trp Glu Val Ala Ile Phe Gly Pro Pro Asn Thr Tyr Tyr Glu Gly Gly Tyr Phe Lys Ala Arg Leu Lys Phe Pro Ile Asp Tyr Pro Tyr Ser Pro Pro Ala Phe Arg Phe Leu Thr Lys Met Trp His Pro Asn Ile Tyr Glu Thr Gly Asp Val Cys Ile Ser Ile Leu His Pro Pro Val Asp Asp Pro Gln Ser Gly Glu Leu Pro Ser Glu Arg Trp Asn 100 105 Pro Thr Gln Asn Val Arg Thr Ile Leu Leu Ser Val Ile Ser Leu Leu 115 120

Asn Glu Pro Asn Thr Phe Ser Pro Ala Asn Val Asp Ala Ser Val Met

395

130 135 Tyr Arg Lys Trp Lys Glu Ser Lys Gly Lys Asp Arg Glu Tyr Thr Asp 150 155 Ile Ile Arg Lys Gln Val Leu Gly Thr Arg Trp Thr Arg Val Asn Gly 165 170 Val Lys Val Pro Thr Thr Leu Ala Glu Tyr Cys Val Lys Thr Lys Ala 185 Pro Ala Pro Asp Glu Gly Ser Asp Leu Phe Tyr Asp Asp Tyr Tyr Glu 195 200 205 Asp Gly Glu Val Glu Glu Glu Ala Asp Ser Cys Phe Gly Asp Asp Glu 215 220 Asp Asp Ser Gly Thr Glu Glu Ser 225 230 <210> 447 <211> 356 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (12) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (53) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (191) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (263) <223> Xaa equals any of the naturally occurring L-amino acids <400> 447 Cys Ser Pro Pro Pro Pro Pro Ala Ala Ala Ala Xaa Ala Ala Ala Ala

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Ala	Met	Ala	Gln 20	Tyr	Lys	Gly	Ala	Ala 25	Ser	Glu	Ala	Gly	Arg 30	Ala	Met
His	Leu	Met 35	Lys	Lys	Arg	Glu	Lys 40	Gln	Arg	Glu	Gln	Met 45	Glu	Gln	Met
Lys	Gln 50	Arg	Ile	Xaa	Glu	Glu -55	Asn	Ile	Met	Lys	Ser 60	Asn	Ile	Asp	Lys
Lys 65	Phe	Ser	Ala	His	Tyr 70	Asp	Ala	Val	Glu	Ala 75	Glu	Leu	Lys	Ser	Ser 80
Thr	Val	Gly	Leu	Val 85	Thr	Leu	Asn	Asp	Met 90	Lys	Ala	Lys	Gln	Glu 95	Ala
Leu	Val	Lys	Glu 100	Arg	Glu	Lys	Gln	Leu 105	Ala	Lys	Lys	Glu	Gln 110	Ser	Lys
Glu	Leu	Gln 115	Met	Lys	Leu	Glu	Lys 120	Leu	Arg	Glu	Lys	Glu 125	Arg	Lys	Lys
Glu	Ala 130	Lys	Arg	Lys	Ile	Ser 135	Ser	Leu	Ser	Phe	Thr 140	Leu	Glu	Glu	Glu
Glu 145	Glu	Gly	Gly	Glu	Glu 150	Glu	Glu	Glu	Ala	Ala 155	Met	Tyr	Glu	Glu	Glu 160
Met	Glu	Arg	Glu	Glu 165	Ile	Thr	Thr	Lys	Lys 170	Arg	Lys	Leu	Gly	Lys 175	Asn
Pro	Asp	Val	Asp 180	Thr	Ser	Phe	Leu	Pro 185	Asp	Arg	Asp	Arg	Glu 190	Xaa	Glu 、
Glu	Asn	Arg 195	Leu	Arg	Glu	Glu	Leu 200	Arg	Gln	Glu	Trp	Glu 205	Ala	Lys	Gln
Glu	Lys 210	Ile	Lys	Ser	Glu	Glu 215	Ile	Glu	Ile	Thr	Phe 220	Ser	Tyr	Trp	Asp
Gly 225	Ser	Gly	His	Arg	Arg 230	Thr	Val	Lys	Met	Arg 235	Lys	Gly	Asn	Thr	Met 240
Gln	Gln	Phe	Leu	Gln 245	Lys	Ala	Leu	Glu	Ile 250	Leu	Arg	Lys	Asp	Phe 255	Ser
Glu	Leu	Arg	Ser 260	Ala	Gly	Xaa	Glu	Gln 265	Leu	Met	Tyr	Ile	Lys 270	Glu	Asp
leu	Tle	Tle	Pro	нія	Hig	His	Ser	Phe	Tvr	Asp	Phe	Ile	Val	Thr	Lvs

275 280 285

Ala Arg Gly Lys Ser Gly Pro Leu Phe Asn Phe Asp Val His Asp Asp 290 295 300

Val Arg Leu Leu Ser Asp Ala Thr Val Glu Lys Asp Glu Ser His Ala 305 310 315 320

Gly Lys Val Val Leu Arg Ser Trp Tyr Glu Lys Asn Lys His Ile Phe 325 330 335

Pro Ala Ser Arg Trp Glu Pro Tyr Asp Pro Glu Lys Lys Trp Asp Lys 340 345 350

Tyr Thr Ile Arg 355

<210> 448

<211> 88

<212> PRT

<213> Homo sapiens

<400> 448

Lys Thr His Lys Met Cys Asp Ala Phe Val Gly Thr Trp Lys Leu Val 1 5 10 15

Ser Ser Glu Asn Phe Asp Asp Tyr Met Lys Glu Val Gly Val Gly Phe $20 \hspace{1cm} 25 \hspace{1cm} 30$

Ala Thr Arg Lys Val Ala Gly Met Ala Lys Pro Asn Met Ile Ile Ser $35 \hspace{1cm} 40 \hspace{1cm} 45$

Val Asn Gly Asp Val Ile Thr Ile Lys Ser Glu Ser Thr Phe Lys Asn 50 55 60

Thr Glu Ile Ser Phe Ile Leu Gly Gln Glu Phe Asp Glu Ala Leu Gln 65 70 75 80

Met Thr Gly Lys Ser Arg Ala Pro 85

<210> 449

<211> 171

<212> PRT

<213> Homo sapiens

<220>

398

<221> SITE

<222> (72)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

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<222> (132)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 449

Leu Ile Leu Val Leu Met Phe Val Val Trp Met Lys Arg Arg Asp Lys

1 10 15

Glu Arg Gln Ala Lys Gln Leu Leu Ile Asp Pro Glu Asp Asp Val Arg 20 25 30

Asp Asn Ile Leu Lys Tyr Asp Glu Glu Gly Gly Glu Glu Asp Gln 35 40 45

Asp Tyr Asp Leu Ser Gln Leu Gln Gln Pro Asp Thr Val Glu Pro Asp 50 55 60

Ala Ile Lys Pro Val Gly Ile Xaa Arg Met Asp Glu Arg Pro Ile His 65 70 75 80

Ala Glu Pro Gln Tyr Pro Val Arg Ser Ala Ala Pro His Pro Gly Asp 85 90 95

Ile Gly Asp Phe Ile Asn Glu Gly Leu Lys Ala Ala Asp Asn Asp Pro
100 105 110

Thr Ala Pro Pro Tyr Asp Ser Leu Leu Val Phe Asp Tyr Glu Gly Ser 115 120 125

Gly Ser Thr Xaa Gly Ser Leu Ser Ser Leu Asn Ser Ser Ser Gly
130 135 140

Gly Glu Gln Asp Tyr Asp Tyr Leu Asn Asp Trp Gly Pro Arg Phe Lys 145 150 155 160

Lys Leu Ala Asp Met Tyr Gly Gly Gly Asp Asp 165 170

<210> 450

<211> 34

<212> PRT

<213> Homo sapiens

<400> 450

Lys Val Lys Ala Cys Cys Lys Asp Ile Phe Phe Leu Leu Glu Gly 5 10

Asn Thr Lys Arg Lys Ile Ser Phe Phe His Gly Ala Phe Asp Asn Phe

Ser Leu

<210> 451

<211> 148

<212> PRT

<213> Homo sapiens

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<222> (43)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (89)

<223> Xaa equals any of the naturally occurring L-amino acids

Arg Thr Leu His Pro Ala Thr Gly Pro Arg Ala Arg Pro Pro Arg Gly

Trp Arg Arg Leu Cys Ala Gln Gly Pro Ala Pro Asp Trp Asp Pro

Gly Val Pro Pro Gly Leu Ala Ser Cys Gly Xaa Thr Val Trp Leu His

Phe Ser Asp Pro Ser Leu Gly Arg Lys Val Lys Glu Thr Gly Pro Ala

Ser Ala Phe Gly Leu Trp Phe Leu Asp Arg Val Leu Ser Pro Ser Pro

Pro Ser Ser Pro Asn Leu Ser His Xaa Arg Pro Leu Pro Ala Ala Pro 90

Ser Leu Leu Gly Ile Gly Ser Pro Glu Pro Pro Ser Pro Glu Pro Pro

Thr Pro Leu Pro Gly Pro Cys Gly Cys Trp Ala Ser His Leu Lys Glu 120 125

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Gly Lys Val Val Gln Pro Glu Pro Val Glu Gln Cys Pro Val Trp Pro
                          135
                                              140
      130
  Pro Lys Pro Lys
  145
  <210> 452
  <211> 83
  <212> PRT
  <213> Homo sapiens
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  <223> Xaa equals any of the naturally occurring L-amino acids
  <220>
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  <220>
  <221> SITE
  <222> (79)
  <223> Xaa equals any of the naturally occurring L-amino acids
  <400> 452
  Asp Ser His Arg Pro Arg Ala Met Arg Ala Leu Trp Val Leu Gly Leu
                                      10
                                                           15
Ser Cys Xaa Leu Leu Thr Phe Gly Ser Val Arg Xaa Asp Asp Glu Val
               20
  Asp Val Asp Gly Thr Val Glu Glu Asp Leu Gly Lys Ser Arg Glu Gly
                               40
  Ser Arg Thr Asp Asp Glu Val Val Gln Arg Glu Glu Glu Ala Ile Xaa
       50
                           55
```

Val Gly Trp Ile Lys Cys Ile Pro Asn Lys Arg Thr Xaa Glu Xaa Lys 75 70 Ser Arg Lys

<210> 453

<211> 240

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (234)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 453

Gly Trp Leu Pro Cys Gly Ser Ser Val Val Pro Ala Thr Pro Gly Ser

Pro Pro Ser Arg Phe Trp Leu Leu Pro Ala Met Ala Leu Arg Val Leu 20 25

Leu Leu Thr Ala Leu Thr Leu Cys His Gly Phe Asn Leu Asp Thr Glu 40

Asn Ala Met Thr Phe Gln Glu Asn Ala Arg Gly Phe Gly Gln Ser Val 55

Val Gln Leu Gln Gly Ser Arg Val Val Val Gly Ala Pro Gln Glu Ile 65

Val Ala Ala Asn Gln Arg Gly Ser Leu Tyr Gln Cys Asp Tyr Ser Thr

Gly Ser Cys Glu Pro Ile His Leu Gln Val Pro Val Glu Ala Val Asn 105

Met Ser Leu Gly Leu Ser Leu Ala Ala Thr Thr Ser Pro Pro Gln Leu 115· 120

Leu Ala Cys Gly Pro Thr Val His Gln Thr Cys Ser Glu Asn Thr Tyr 135

Val Lys Gly Leu Cys Phe Leu Phe Gly Ser Asn Leu Arg Gln Gln Pro 145 150

Gln Lys Phe Pro Glu Ala Leu Arg Gly Cys Pro Gln Glu Asp Ser Asp 165 170

IleAlaPheLeu 180IleAsp GlySer GlySer GlySer IleIlePro His Asp Phe 190ArgArgMet 195LysGluPheValSer Thr ValMet GluGlnLeu LysLysSerLysThr Leu PheSer Leu 215Met GlnTyrSer GluGluPheArgIleHisPheThr SerLysSer Ser ArgThr XaaLeu Thr GlnAsp HisTrp 240

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<210> 454
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<212> PRT
<213> Homo sapiens
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<222> (206)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
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<222> (227)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
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<222> (229)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
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<222> (239)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 454
Lys Trp Cys Ser Trp Thr Leu Leu Lys Ile Trp Glu Val Thr Cys Thr
Trp Lys Leu Pro Thr Leu Ala Lys Phe Ser Pro Tyr Leu Gly Gln Met
             20
```

Ile Asn Leu Arg Arg Leu Leu Ser His Ile His Ala Ser Ser Tyr

			45					40					35		
Glr	Ser	Thr	Phe	Gln 60	Ala	Ile	Tyr	Gln	Glu 55	Glu	Lys	Glu	Pro	Ser 50	Ile
Phe 80	Leu	Ser	Asp	Val	Туг 75	Leu	Leu	Gln	Leu	Cys 70	Gln	Leu	Ser	Leu	Phe 65
	Asn 95	Met	Val	His	Arg	Leu 90	Leu	Gln	Asp	Leu	Arg 85	Gly	Arg	Leu	Phe
Val	Asp	Gly 110	Glu	Ser	Leu	Arg	Cys 105	Asn	Thr	Ile	Ser	Leu 100	Thr	Glu	Leu
Ser	Leu	Val	Ser 125	Leu	Gln	Ser	Val	Ser 120	Pro	Ser	Gln	ser	Leu 115	His	Met
Ala	Gln	Leu	Pro	Glu 140	Pro	Ser	Val	Asp	Thr 135	Leu	Met	Val	Gly	Ser 130	Leu
Glu 160	Asp	Phe	Val	Leu	Asp 155	Gln	Leu	Thr	Ala	Ser 150	Ala	Arg	Glu	Leu	Leu 145
	Leu 175	Ser	Pro	Leu	Leu	Ala 170	Leu	Leu	Gln	Asp	Asp 165	Thr	Ile	Gly	Cys
Ser	Ile	Ser 190	Asn	Gly	Tyr	Phe	ser 185	Leu	Thr	Thr	Leu	Gln 180	Ser	Cys	His
Asn	Ser	Xaa	Gly 205	Ile	Leu	His	Gln	Leu 200	Leu	Ser	Gln	Leu	Ala 195	Ser	Ile
Ile	Asp	Glu	Tyr	Ser 220	Glu	Leu	Pro	Val	Pro 215	Tyr	Leu	Val	His	Thr 210	Leu
Gln 240	Xaa	Gln	Cys	Ala	ser 235	Leu	Leu	Arg	Glu	Leu 230	Xaa	Leu	Xaa	Gly	His 225
												Val	Ala	Val	Gly

<210> 455

<211> 195

<212> PRT

<213> Homo sapiens

<400> 455

His Glu Gly Thr Gln Ser Phe Val Phe Gln Arg Glu Glu Ile Ala Gln $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$

404

Leu Ala Arg Gln Tyr Ala Gly Leu Asp His Glu Leu Ala Phe Ser Arg
20 25 30

Leu Ile Val Glu Leu Arg Arg Leu His Pro Gly His Val Leu Pro Asp 35 40 45

Glu Glu Leu Gln Trp Val Phe Val Asn Ala Gly Gly Trp Met Gly Ala 50 60

Met Cys Leu Leu His Ala Ser Leu Ser Glu Tyr Val Leu Leu Phe Gly 65 70 75 80

Thr Ala Leu Gly Ser Arg Gly His Ser Gly Arg Tyr Trp Ala Glu Ile 85 90 95

Ser Asp Thr Ile Ile Ser Gly Thr Phe His Gln Trp Arg Glu Gly Thr 100 105 110

Thr Lys Ser Glu Val Phe Tyr Pro Gly Glu Thr Val Val His Gly Pro
115 120 125

Gly Glu Ala Thr Ala Val Glu Trp Gly Pro Asn Thr Trp Met Val Glu 130 135 140

Tyr Gly Arg Gly Val Ile Pro Ser Thr Leu Ala Phe Ala Leu Ala Asp 145 150 155 160

Thr Val Phe Ser Thr Gln Asp Phe Leu Thr Leu Phe Tyr Thr Leu Arg 165 170 175

Ser Tyr Ala Arg Gly Leu Arg Leu Glu Leu Thr Thr Tyr Leu Phe Gly 180 185 190

Gln Asp Pro 195

<210> 456

<211> 36

<212> PRT

<213> Homo sapiens

<400> 456

Leu Val Thr Leu Leu His Ala Met Gln Ala Arg Asp Lys Thr Leu Gly

Leu Ala Thr Leu Cys Ile Gly Gly Gly Gly Gly Ile Ala Met Val Ile 20 25 30

Glu Arg Leu Asn 35

<210> 457

<211> 152

<212> PRT

<213> Homo sapiens

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<222> (86)

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<220>

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<222> (114)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 457

Val Thr Ala Ala Ala Ser Val Arg Ala Leu Gln Val Thr Val Ala Gly
1 10 15

Leu Leu Val Phe Phe Leu Phe Gly Ala Pro Leu Asp Ser Leu Pro
20 25 30

Ser Met Lys Ala Leu Ser Pro Val Arg Gly Cys Tyr Glu Ala Val Cys 35 40 45

Cys Leu Ser Glu Arg Ser Leu Ala Ile Ala Arg Gly Arg Gly Lys Gly 50 55 60

Pro Ala Ala Glu Glu Pro Leu Ser Leu Leu Asp Asp Met Asn His Cys 65 70 75 80

Tyr Ser Arg Leu Arg Xaa Leu Val Pro Gly Val Pro Arg Gly Thr Gln
85 90 95

Leu Ser Gln Val Glu Ile Leu Gln Arg Val Ile Asp Tyr Ile Leu Asp 100 105 110

Leu Xaa Val Val Leu Ala Glu Pro Ala Pro Gly Pro Pro Asp Gly Pro
115 120 125

His Leu Pro Ile Gln Thr Ala Glu Leu Ala Pro Glu Leu Val Ile Ser 130 135 140

Asn Asp Lys Arg Ser Phe Cys His 145 150

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<211> 31
<212> PRT
<213> Homo sapiens
<220>
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<222> (17)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (25)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (31)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 458
Leu Leu Asn Asn Phe Ile Phe Leu Glu Thr His Tyr Leu Trp Ala Cys
Xaa Thr Trp Thr Ile Trp Pro Asn Xaa Leu Asp Lys Lys Gly Xaa
             20
                                 25
<210> 459
<211> 157
<212> PRT
<213> Homo sapiens
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<223> Kaa equals any of the naturally occurring L-amino acids
<220>
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<223> Xaa equals any of the naturally occurring L-amino acids
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<210> 458

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<223> Xaa equals any of the naturally occurring L-amino acids
<400> 459
Asp Pro Arg Val Arg Glu Thr Thr Val Lys Ala Arg Ala Arg Ser Gln
His Ala Gly Gly Pro Glu Leu Gly Leu Ser Gln Xaa Tyr Val Thr Pro
Arg Arg Pro Phe Glu Lys Ser Arg Leu Asp Gln Glu Leu Lys Leu Ile
Gly Glu Tyr Gly Leu Arg Asn Lys Arg Glu Val Trp Arg Val Lys Phe
Thr Leu Ala Lys Ile Arg Lys Xaa Ala Arg Glu Leu Leu Thr Leu Asp
Glu Lys Asp Pro Arg Arg Leu Phe Glu Gly Asn Ala Leu Leu Arg Arg
Leu Val Arg Ile Gly Val Leu Asp Glu Gly Lys Met Lys Leu Asp Tyr
                                105
Ile Leu Gly Leu Lys Met Arg Ile Leu Gly Glu Xaa Ser Ala Asp Pro
Gly Xaa Ser Ser Trp Gly Trp Pro Ile His Pro Pro Cys Pro Val Leu
                       135
Ile Arg Gln Ala Thr Gln Val Arg Lys Gln Val Val Asn
<210> 460
<211> 136
<212> PRT
<213> Homo sapiens
<220>
<221> SITE
<222> (119)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
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<222> (130)
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<223> Xaa equals any of the naturally occurring L-amino acids

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<220>
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<222> (135)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 460
Ile Trp Ala Pro Phe Pro His His Gln Gly Ser Gly Ser Gln Val Ser
Ser Tyr Gly Thr Gly Ala Leu Lys Ser His Ile Met Ala Ala Lys Ala
             20
                                 25
Val Ala Asn Thr Met Arg Thr Ser Leu Gly Pro Asn Gly Leu Asp Lys
Met Met Val Asp Lys Asp Gly Asp Val Thr Val Thr Asn Asp Gly Ala
                       55
Thr Ile Leu Ser Met Met Asp Val Asp His Gln Ile Ala Lys Leu Met
                                  75
                    70
 65
Val Glu Leu Ser Lys Ser Gln Asp Asp Glu Ile Gly Asp Gly Asp His
                                     90
                 85
Gly Gly Cys Pro Gly Arg Arg Pro Ala Gly Arg Arg Pro Ser Ser
                               105
Cys Trp Thr Ala Ala Phe Xaa Arg Ser Gly Ser Pro Thr Val Thr Ser
        115
                                               125
                           120
Arg Xaa Pro Ala Leu Ala Xaa Glu
   130
                       135
<210> 461
<211> 390
<212> PRT
<213> Homo sapiens
<220>
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<222> (11)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
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<222> (14)
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>
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<223> Xaa equals any of the naturally occurring L-amino acids
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<223> Xaa equals any of the naturally occurring L-amino acids
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<222> (386)
<223> Xaa equals any of the naturally occurring L-amino acids
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<222> (387)
<223> Xaa equals any of the naturally occurring L-amino acids
Cys Gly Asn Trp Trp Val Pro Arg Ala Gly Xaa Asn Trp Xaa Arg Gly
Ser Arg Phe Leu Phe Val Asp Arg Cys Asp Arg His Leu Thr Met Gln
                                 25
Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val Glu
         35
                             40
Pro Ser Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp Lys Glu
Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu
                     70
Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu Ser Thr
                 85
                                    90
Leu His Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe Val Lys
                                105
Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val Glu Pro Ser Asp Thr
        115
                            120
                                                125
```

Ile	Glu 130	Asn	Val	Lys	Ala	Lys 135	Ile	Gln	Asp	Lys	140	Gly	IIe,	Pro	Pro
Asp 145	Gln	Gln	Arg	Leu	Ile 150	Phe	Ala	Gly	Lys	Gln 155	Leu	Glu	Asp	Gly	Arg 160
Thr	Leu	Ser	Asp	Tyr 165	Asn	Ile	Gln	Lys	Glu 170	Ser	Thr	Leu	His	Leu 175	Val
Leu	Arg	Leu	Arg 180	Gly	Gly	Met	Gln	Ile 185	Phe	Val	Lys	Thr	Leu 190	Thr	Gly
Lys	Thr	Ile 195	Thr	Leu	Glu	Val	Glu 200	Pro	Ser	Asp	Thr	11e 205	Glu	Asn	Val
	210				Asp	215					220				
225					Lys 230					235					240
				245	Glu				250					255	
-	-		260		Phe		-	265			_	-	270		
		275			Ser		280					285			
	290	-		_	Ile	295					300				
305					Asp 310 His					315					320
-				325	Leu				330					335	
			340		Glu			345					350		
		355			Glu		360					365			
	370		Pro			375	204			204	380	-,0			_, ~
385					390										

PCT/US00/05881 WO 00/55173

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<210> 462
<211> 171
<212> PRT
<213> Homo sapiens
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<222> (74)
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<223> Xaa equals any of the naturally occurring L-amino acids
<400> 462
Cys Ser Thr Val Arg Ile Pro Gly Ser Thr His Ala Ser Gly Leu Ser
        5
                                   10
Arg Arg Ala Ser Pro Val Tyr Leu Ala Ser Met Ser Gly Arg Gly Lys
            20
Thr Gly Gly Lys Ala Arg Ala Lys Ala Lys Ser Arg Ser Ser Arg Ala
                            40
Gly Leu Gln Phe Pro Val Gly Arg Val His Arg Leu Leu Arg Lys Gly
    50 55
His Tyr Ala Glu Arg Val Gly Ala Gly Xaa Pro Val Tyr Leu Ala Ala
                    70
65
Val Leu Glu Tyr Leu Thr Ala Glu Ile Leu Glu Leu Ala Gly Asn Ala
                                    90
                85
Ala Arg Asp Asn Lys Lys Thr Arg Ile Ile Pro Arg His Leu Gln Leu
           100
                               105
Ala Ile Arg Asn Asp Glu Glu Leu Asn Lys Leu Leu Gly Gly Val Thr
       115
                           120
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Ile Ala Gln Gly Arg Arg Xaa Ala Gln His Pro Gly Arg Xaa Cys Cys Pro Arg Arg Pro Ala Pro Pro Trp Gly Arg Xaa Pro Phe Gly Gln 150 Glu Arg Ala Thr Lys Ala Ser Gln Gly Val Leu 165 <210> 463 <211> 433 <212> PRT <213> Homo sapiens <400> 463 Arg Val Arg Ala Pro Pro Arg Pro Pro Leu Gly Pro Ser Arg Pro Ser His His Val His Pro Leu Gln Leu Pro Gly Ile Arg Glu Val Thr Ile Asn Gln Ser Leu Leu Ala Pro Leu Arg Leu Asp Ala Asp Pro Ser Leu 40 45 Gln Arg Val Arg Gln Glu Glu Ser Glu Gln Ile Lys Thr Leu Asn Asn 55 Lys Phe Ala Ser Phe Ile Asp Lys Val Arg Phe Leu Glu Gln Gln Asn Lys Leu Leu Glu Thr Lys Trp Thr Leu Leu Gln Glu Gln Lys Ser Ala Lys Ser Ser Arg Leu Pro Asp Ile Phe Glu Ala Gln Ile Ala Gly Leu . Arg Gly Gln Leu Glu Ala Leu Gln Val Asp Gly Gly Arg Leu Glu Ala 120 Glu Leu Arg Ser Met Gln Asp Val Glu Asp Phe Lys Asn Lys Tyr 130 Glu Asp Glu Ile Asn Arg Arg Thr Ala Ala Glu Asn Glu Phe Val Val 150 Leu Lys Lys Asp Val Asp Ala Ala Tyr Met Ser Lys Val Glu Leu Glu

Ala	Lys	Val	Asp 180	Ala	Leu	Asn	Asp	Glu 185	Ile	Asn	Phe	Leu	Arg 190	Thr	Leu
Asn	Glu	Thr 195	Glu	Leu	Thr	Glu	Leu 200	Gln	Ser	Gln	Ile	Ser 205	Asp	Thr	Ser
Val	Val 210	Leu	Ser	Met	Asp	Asn 215	Ser	Arg	Ser	Leu	Asp 220	Leu	Asp	Gly	Ile
Ile 225	Ala	Glu	Val	Lys	Ala 230	Gln	Tyr	Glu	Glu	Met 235	Ala	Lys	Cys	Ser	Arg 240
Ala	Glu	Ala	Glu	Ala 245	Trp	Tyr	Gln	Thr	Lys 250	Phe	Glu	Thr	Leu	Gln 255	Ala
Gln	Ala	Gly	Lys 260	His	Gly	Asp	Asp	Leu 265	Arg	Asn	Thr	Arg	Asn 270	Glu	Ile
Ser	Glu	Met 275	Asn	Arg	Ala	Ile	Gln 280	Arg	Leu	Gln	Ala	Glu 285	Ile	Asp	Asn
Ile	Lys 290	Asn	Gln	Arg	Ala	Lys 295	Leu	Glu	Ala	Ala	Ile 300	Ala	Glu	Ala	Glu
Glu 305	Arg	Gly	Glu	Leu	Ala 310	Leu	Lys	Asp	Ala	Arg 315	Ala	Lys	Gln	Glu	Glu 320
Leu	Glu	Ala	Ala	Leu 325	Gln	Arg	Ala	Lys	Gln 330	Asp	Met	Ala	Arg	Gln 335	Leu
Arg	Glu	Tyr	Gln 340	Glu	Leu	Met	Ser	Val 345	Lys	Leu	Ala	Leu	Asp 350	Ile	Glu
Ile	Ala	Thr 355	Tyr	Arg	Lys	Leu	Leu 360	Glu	Gly	Glu	Glu	Ser 365	Arg	Leu	Ala
Gly	Asp 370	Gly	Val	Gly	Ala	Val 375	Asn	Ile	Ser	Val	Met 380	Asn	Ser	Thr	Gly
31y 385	Ser	Ser	Ser	Gly	Gly 390	Gly	Ile	Gly	Leu	Thr 395	Leu	Gly	Gly	Thr	Met 400
Gly	Ser	Asn	Ala	Leu 405	Ser	Phe	Ser	Ser	Ser 410	Ala	Gly	Pro	Gly	Leu 415	Leu
Lys	Ala	Tyr	Ser 420		Arg	Thr	Ala	Ser 425	Ala	Ser	Arg	Arg	Ser 430	Ala	Arg

Asp

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<211> 121
<212> PRT
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<400> 464
Gly Ser Gly Cys Val Phe Ala Ile Leu Gly Arg Arg Cys Ser Arg Pro
                                      10
Trp Arg Ile Trp Pro Gly Glu Pro Leu Gln Arg Ala Pro Pro Ala Ala
Gly Thr Arg Trp Pro His Gly His Arg Ser Ser Pro Val Gly Thr Pro
         35
                                                 45
Gly Xaa Ala Pro Asn Val Pro Ala Ile Trp Gln Gln Pro Leu Trp Xaa
     50
                         55
Glu Tyr Ser Cys Glu Tyr Gly Ser Met Lys Phe Tyr Ala Leu Cys Gly
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415

65 70 75 80

Leu Asp Leu Val Lys Cys Arg Met Gln Val Asp Pro Gln Xaa Tyr Lys 100 105 110

Gly Xaa Xaa Asn Xaa Ile Leu Ile Asn 115 120

<210> 465

<211> 68

<212> PRT

<213> Homo sapiens

<400> 465

Arg Ile Pro Ala Pro Ala Ser Ser Arg His Ser Gly Gly Arg Cys Ala 1 5 10 15

Ala Gly Pro Arg Gly Pro Pro Ala Thr Ala Ser Arg Ala Leu Arg Ala
20 25 30

Val His Arg Pro Leu Asp Ala Ala Arg Gly Arg Thr Gly Ser Thr Ser 35 40 45

His Leu Cys Ser Ser Ser Tyr Thr Ile Gly Cys Leu Leu Trp Phe Ser 50 55 60

Gln Lys Ala Met 65

<210> 466

<211> 224

<212> PRT

<213> Homo sapiens

<400> 466

Ala Thr Ile Leu Glu Arg Glu Ala Glu Gln Ser Arg Leu Gly Ala Thr 1 5 10 15

Glu Arg Ala Ala Ala Ala Met Asn Pro Glu Tyr Asp Tyr Leu Phe $20 \hspace{1cm} 25 \hspace{1cm} 30$

Lys Leu Leu Ile Gly Asp Ser Gly Val Gly Lys Ser Cys Leu Leu 35 40 45

416

Leu Arg Phe Ala Asp Asp Thr Tyr Thr Glu Ser Tyr Ile Ser Thr Ile
50 55 60

Gly Val Asp Phe Lys Ile Arg Thr Ile Glu Leu Asp Gly Lys Thr Ile 65 70 75 80

Lys Leu Gln Ile Trp Asp Thr Ala Gly Gln Glu Arg Phe Arg Thr Ile $85 \hspace{1cm} 90 \hspace{1cm} 95$

Thr Ser Ser Tyr Tyr Arg Gly Ala His Gly Ile Ile Val Val Tyr Asp 100 105 110

Val Thr Asp Gln Glu Ser Tyr Ala Asn Val Lys Gln Trp Leu Gln Glu 115 120 125

Ile Asp Arg Tyr Ala Ser Glu Asn Val Asn Lys Leu Leu Val Gly Asn 130 135 140

Lys Ser Asp Leu Thr Thr Lys Lys Val Val Asp Asn Thr Thr Ala Lys 145 150 155 160

Glu Phe Ala Asp Ser Leu Gly Ile Pro Phe Leu Glu Thr Ser Ala Lys 165 170 175

Asn Ala Thr Asn Val Glu Gln Ala Phe Met Thr Met Ala Ala Glu Ile 180 185 190

Lys Lys Arg Met Gly Pro Gly Ala Ala Ser Gly Gly Glu Arg Pro Asn 195 200 205

Leu Lys Ile Asp Ser Thr Pro Val Lys Pro Ala Gly Gly Gly Cys Cys 210 215 220

<210> 467

<211> 76

<212> PRT

<213> Homo sapiens

<400> 467

Ser Glu Ala Pro Gly Glu Ser Val Gly Thr Thr Pro Glu Ala Gln Met

1 5 10 15

Lys Thr Gly Pro Phe Ala Glu His Ser Asn Gln Leu Trp Asn Ile Ser 20 25 30

Ala Val Pro Ser Trp Ser Lys Val Asn Gln Gly Leu Ile Arg Met Tyr

417

45 35 40 Lys Ala Glu Cys Leu Glu Lys Phe Pro Val Ile Gln His Phe Lys Phe 55 Gly Ser Leu Leu Pro Ile His Pro Val Thr Ser Gly 70 <210> 468 <211> 111 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (31) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (35) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (47) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (49) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (78) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (97) <223> Xaa equals any of the naturally occurring L-amino acids <400> 468 Ser Leu Ala Arg Thr Gly Pro Arg Ser Leu Ala Arg Pro Cys Arg Arg 5 10 15 Arg Pro Ala His Arg His Pro Leu Gln Pro Cys Pro Pro Gly Xaa Cys

25

Pro Arg Xaa Pro Thr Ala Asp Val Arg Arg Pro Arg His Arg Xaa Arg Xaa Glu Leu His Ala His Asn Val Thr Ser Pro Pro Ala Pro Thr Ala 55 Trp Ala Ala Pro Ala Pro Gln His Gln Pro Gln Pro Leu Xaa Leu Val 70 Pro Gly Arg Arg Val Cys Ser Arg Leu Leu Pro Arg Cys Ala Cys Gly 90 Xaa Cys Cys Pro Gly Val Ala Leu Ala Gly Arg Ile Pro Trp Asn 105 <210> 469 <211> 459 <212> PRT <213> Homo sapiens <400> 469 Pro Arg Val Arg Pro Arg Val Arg Pro Arg Val Arg Leu Ser Ser Pro Ser Pro Val Cys Leu Pro Pro Ala Ala Ala Thr Met Thr Thr Ser Ile 20 Arg Gln Phe Thr Ser Ser Ser Ile Lys Gly Ser Ser Gly Leu Gly Gly Gly Ser Ser Arg Thr Ser Cys Arg Leu Ser Gly Gly Leu Gly Ala 55 Gly Ser Cys Arg Leu Gly Ser Ala Gly Gly Leu Gly Ser Thr Leu Gly Gly Ser Ser Tyr Ser Ser Cys Tyr Ser Phe Gly Ser Gly Gly Tyr Gly Ser Ser Phe Gly Gly Val Asp Gly Leu Leu Ala Gly Gly Glu Lys 100 Ala Thr Met Gln Asn Leu Asn Asp Arg Leu Ala Ser Tyr Leu Asp Lys 115 120 Val Arg Ala Leu Glu Glu Ala Asn Thr Glu Leu Glu Val Lys Ile Arg

145	Trp	Tyr	GIN	Arg	150	Ala	PIO	GIŞ	PIO	155	Arg	wab	ıyı	Ser	160
Tyr	туг	Arg	Thr	Ile 165	Glu	Glu	Leu	Gln	Asn 170	Lys	Ile	Leu	Thr	Ala 175	Thr
Val	Asp	Asn	Ala 180	Asn	Ile	Leu	Leu	Gln 185	Ile	Asp	Asn	Ala	Arg 190	Leu	Ala
Ala	Asp	Asp 195	Phe	Arg	Thr	Lys	Phe 200	Glu	Thr	Glu	Gln	Ala 205	Leu	Arg	Leu
Ser	Val 210	Glu	Ala	Asp	Ile	Asn 215	Gly	Leu	Arg	Arg	Val 220	Leu	Asp	Glu	Leu
Thr 225	Leu	Ala	Arg	Ala	Asp 230	Leu	Glu	Met	Gln	11e 235	Glu	Asn	Leu	Lys	Glu 240
Glu	Leu	Ala	туг	Leu 245	Lys	Lys	Asn	His	Glu 250	Glu	Glu	Met	Asn	Ala 255	Leu
_	_		260					265					270	Ala	
		275					280					285		Tyr	
	290					295					300			Phe	
305					310					315				Leu	320
				325					330					Gln 335	
			340					345					350	Leu	
Gly	Asn	Leu 355	Ala	Glu	Thr	Glu	Asn 360	Arg	Tyr	Cys	Val	Gln 365	Leu	Ser	Gln
	370					375					380			Leu	
Cys 385	Glu	Met	Glu	Gln	Gln 390	Asn	Gln	Glu	Tyr	Lys 395	Ile	Leu	Leu	Asp	Val 400
Lys	Thr	Arg	Leu	Glu 405	Gln	Glu	Ile	Ala	Thr 410	Tyr	Arg	Arg	Leu	Leu 415	Glu

Gly Glu Asp Ala His Leu Thr Gln Tyr Lys Lys Glu Pro Val Thr Thr 420 425 430

Arg Gln Val Arg Thr Ile Val Glu Glu Val Gln Asp Gly Lys Val Ile 435 440 445

Ser Ser Arg Glu Gln Val His Gln Thr Thr Arg 450 455

<210> 470

<211> 158

<212> PRT

<213> Homo sapiens

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<222> (158)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 470

Pro Pro Pro Pro Pro Pro Pro Glu Leu Cys Ser Met Ala Ser Arg Arg

1 5 10 15

Met Glu Thr Lys Pro Val Ile Thr Cys Leu Lys Thr Leu Leu Ile Ile 20 25 30

Tyr Ser Phe Val Phe Trp Ile Thr Gly Val Ile Leu Leu Ala Val Gly 35 40 45

Val Trp Gly Lys Leu Thr Leu Gly Thr Tyr Ile Ser Leu Ile Ala Glu 50 60

Asn Ser Thr Asn Ala Pro Tyr Val Leu Ile Gly Thr Gly Thr Thr Ile 65 70 75 80

Val Val Phe Gly Leu Phe Gly Cys Phe Ala Thr Cys Arg Gly Ser Pro $85 \hspace{1cm} 90 \hspace{1cm} 95$

Trp Met Leu Lys Leu Tyr Ala Met Phe Leu Ser Leu Val Phe Leu Ala 100 105 110

Glu Leu Val Ala Gly Ile Ser Gly Phe Val Phe Arg His Glu Ile Lys 115 120 125

Asp Thr Phe Leu Arg Thr Tyr Thr Asp Ala Met Gln Thr Tyr Asn Gly
130 135 140

PCT/US00/05881 WO 00/55173

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<210> 471
<211> 59
<212> PRT
<213> Homo sapiens
<400> 471
Val Leu Phe Phe Tyr Glu Cys Pro Asn Leu Cys Phe Pro Leu Pro Ser
Gln Thr Val Trp Pro Val Glu Ser Val Trp Phe Val Phe Ile Ser Pro
                                 25
Ser Phe Leu Glu Gln Gly Leu Arg Pro Cys His Ile Ser Tyr Ala Leu
                             40
His Pro Arg Leu Phe Trp Thr Leu Lys Val Asp
                         55
     50
<210> 472
<211> 320
<212> PRT
<213> Homo sapiens
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<223> Xaa equals any of the naturally occurring L-amino acids
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<222> (53)
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<220>
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<222> (105)
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Asp Pro Asp Glu Val Phe Pro Val Cys Leu Pro Leu Thr Gly Asp Ala
                                     10
                  5
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Gly	Glu	Asp	Gly 20	Gly	Lys	Met	Leu	His 25	Leu	Pro	Glu	Trp	Pro 30	Glu	Gln
Pro	Pro	Gly 35	Gly	Pro	Ala	Ala	Leu 40	Gln	Val	Arg	Gly	Ala 45	Glu	Asp	Xaa
Xaa	Leu 50	Ser	Phe	Xaa	Asp	Cys 55	Glu	Ser	Leu	Gln	Ala 60	Val	Phe	Asp	Pro
Ala 65	Ser	Суз	Pro	His	Met 70	Leu	Arg	Ala	Pro	Ala 75	Arg	Val	Leu	Gly	Glu 80
Ala	Val	Leu	Pro	Phe 85	Ser	Pro	Ala	Leu	Ala 90	Glu	Val	Thr	Leu	Gly 95	Ile
Gly	Arg	Gly	Ala 100	Gly	Ser	Ser	Trp	Xaa 105	Tyr	His	Glu	Glu	Glu 110	Ala	Asp
Ser	Thr	Ala 115	Lys	Ala	Met	Val	Thr 120	Glu	Met	Cys	Leu	Gly 125	Glu	Glu	Asp
Phe	Gln 130	Gln	Leu	Gln	Ala	Gln 135	Glu	Gly	Val	Ala	Ile 140	Thr	Phe	Суѕ	Leu
Lys 145	Glu	Phe	Arg	Gly	Leu 150	Leu	Ser	Phe	Ala	Glu 155	Ser	Ala	Asn	Leu	Asn 160
Leu	Ser	Ile	His	Phe 165	Asp	Ala	Pro	Gly	Arg 170	Pro	Ala	Ile	Phe	Thr 175	Ile
Lys	Asp	Ser	Leu 180	Leu	Asp	Gly	His	Phe 185	Val	Leu	Ala	Thr	Leu 190	Ser	Asp
Phr	Asp	Ser 195	His	Ser	Gln	Asp	Leu 200	Gly	Ser	Pro	Glu	Arg 205	His	Gln	Pro
Val	Pro 210	Gln	Leu	Gln	Ala	His 215	Ser	Thr	Pro	His	Pro 220	Asp	Asp	Phe	Ala
Asn 225	Asp	Asp	Ile	Asp	5er 230	Tyr	Met	Ile	Ala	Met 235	Glu _.	Thr	Thr	Ile	Gly 240
Asn	Glu	Gly	Ser	Arg 245	Val	Leu	Pro	Ser	11e 250	Ser	Leu	Ser	Pro	Gly 255	Pro
Gln	Pro	Pro	Lys 260	Ser	Pro	Gly	Pro	ніs 265	Ser	Glu	Glu	Glu	Asp 270	Glu	Ala
Glu	Pro	Ser 275	Thr	Val	Pro	Gly	Thr 280	Pro	Pro	Pro	Lys	Lys 285	Phe	Arg	Ser

423

Leu Phe Phe Gly Ser Ile Leu Ala Pro Val Arg Ser Pro Gln Gly Pro 290 295 300

Ser Leu Cys Trp Arg Lys Thr Val Arg Val Lys Ala Glu Pro Arg Thr 305 310 315 320

<210> 473

<211> 331

<212> PRT

<213> Homo sapiens

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<222> (24)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (283)

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<220>

<221> SITE

<222> (299)

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<220>

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<222> (324)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 473

Pro Pro Cys Ala Val Pro Gly Pro Arg Leu Ser Pro Lys Leu Arg Thr
1 5 10 15

Pro Ser Asn Ser Arg Glu Ser Xaa Ile Cys Val Ser Gly Arg Ala Glu $20 \hspace{1cm} 25 \hspace{1cm} 30$

Ala Leu Thr Phe Arg His Gly Ala Glu Gly Ser Asp Arg Arg Gln 35 40 45

Arg Arg Glu Gly Val Leu Gly Pro Ala Leu Leu Cys Arg Pro Trp Glu 50 60

Val Leu Gly Ala His Glu Val Pro Ser Arg Asn Ile Phe Ser Glu Gln

65					70					75					80
Thr	Ile	Pro	Pro	Ser 85	Ala	Lys	Tyr	Gly	Gly 90	Arg	His	Thr	Val	Thr 95	Met
Ile	Pro	Gly	Asp 100	Gly	Ile	Gly	Pro	Glu 105	Leu	Met	Leu	His	Val 110	Lys	Ser
Val	Phe	Arg 115	His	Ala	Cys	Val	Pro 120	Val	Asp	Phe	Glu	Glu 125	Val	His	Val
Ser	Ser 130	Asn	Ala	Asp	Glu	Glu 135	Asp	Ile	Arg	Asn	Ala 140	Ile	Met	Ala	Ile
Arg 145	Arg	Asn	Arg	Val	Ala 150	Leu	Lys	Gly	Asn	11e 155	Glu	Thr	Asn	His	Asn 160
Leu	Pro	Pro	Ser	His 165	Lys	Ser	Arg	Asn	Asn 170	Ile	Leu	Arg	Thr	Ser 175	Leu
Asp	Leu	Tyr	Ala 180	Asn	Val	Ile	His	Cys 185	Lys	Ser	Leu	Pro	Gly 190	Val	Val
Thr	Arg	His 195	Lys	Asp	Ile	Asp	Ile 200	Leu	Ile	Val	Arg	Glu 205	Asn	Thr	Glu
Gly	Glu 210	Tyr	Ser	Ser	Leu	Glu 215	His	Glu	Ser	Val	Ala 220	Gly	Val	Val	Glu
Ser 225	Leu	Lys	Ile	Ile	Thr 230	Lys	Ala	Lys	Ser	Leu 235	Arg	Ile	Ala	Glu	туг 240
Ala	Phe	Lys	Leu	Ala 245	Gln	Glu	Ser	Gly	Arg 250	Lys	Lys	Val	Thr	Ala 255	Val
His	Lys	Ala	Asn 260	Ile	Met	Lys	Leu	Gly 265	Asp	Gly	Leu	Phe	Leu 270	Gln	Cys
Cys	Arg	Glu 275	Val	Ala	Ala	Arg	Туг 280	Pro	Gln	Xaa	Thr	Phe 285	Glu	Asn	Met
Ile	Val 290	Asp	Asn	Thr	Thr	Met 295	Gln	Leu	Val	Xaa	Arg 300	Pro	Gln	Gln	Phe
Asp 305	Val	Met	Val	Met	Pro 310	Asn	Leu	Tyr	Gly	Asn 315	Ile	Val	Lys	Gln	Cys 320
Leu	Arg	Gly	Xaa	Gly 325	Arg	Gly	Pro	Lys	Leu 330	Val					

PCT/US00/05881 WO 00/55173

425

<210> 474 <211> 30 <212> PRT <213> Homo sapiens <400> 474 Thr Pro Ile Ser Thr Lys Asn Thr Lys Ile Ser Gln Ala Arg Trp Arg 10 Ala His Val Val Pro Ala Thr Arg Glu Ala Asp Ala Glu Glu 25 <210> 475 <211> 124 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (110) <223> Xaa equals any of the naturally occurring L-amino acids <400> 475 Thr Gln Phe Ser Leu Ser Pro Val Glu Thr Ile Tyr Thr Ile Leu Cys 5 10 Ile Asn Val Tyr Thr Leu Pro Ile Cys Ile His Ile Tyr Ile Val Tyr Ile Leu Tyr Met Tyr Arg Cys Val Tyr Val His Ile Tyr Thr His Ala 40 His Asn Lys Ile Arg Cys Ser Leu Gln Ile Gln Met Leu Ile Thr Lys

Pro Asp Ala Thr Gln Thr Ala Ala Glu Glu Thr Arg Leu Asp Ser Cys 70

55

Asn Arg Ser Gln Lys Ile Lys Thr Ala Thr Cys Ser Asp Phe Gly His 90

Phe Cys Met Phe Ile Lys Asn Gly Phe Val Thr Arg Lys Xaa Arg Thr 100 105

Ser Val Ser Glu Lys Gly Arg Trp Gly Glu Pro Ser 120

426

<210> 476 <211> 64 <212> PRT

<213> Homo sapiens

<400> 476

Asn Gly Tyr Leu Val Phe Pro Arg Lys Asn Ser Phe Leu Leu Ile Phe 1 5 10 15

Gly Leu Phe Val Tyr Leu Glu Thr Asn Leu Asp Ser Leu Pro Leu Val 20 25 30

Asp Thr His Ser Lys Arg Thr Leu Leu Ile Lys Thr Val Glu Thr Arg
35 40 45

Asp Gly Gln Val Ile Asn Glu Thr Ser Gln His His Asp Asp Leu Glu 50 55 60

<210> 477

<211> 107

<212> PRT

<213> Homo sapiens

<400> 477

Val Leu Thr Val Asp Ala Arg Asn His Gly Asp Ser Pro His Ser Pro 1 5 10 15

Asp Met Ser Tyr Glu Ile Met Ser Gln Asp Leu Gln Asp Leu Leu Pro 20 25 30

Gln Leu Gly Leu Val Pro Cys Val Val Gly His Ser Met Gly Gly
35 40 45

Lys Thr Ala Met Leu Leu Ala Leu Gln Arg Pro Glu Leu Val Glu Arg 50 55 60

Leu Ile Ala Val Asp Ile Ser Pro Val Glu Ser Thr Gly Val Ser His 65 70 75 80

Phe Ala Thr Tyr Val Ala Ala Met Arg Ala Ile Asn Ile Ala Asp Arg 85 90 95

Leu Ala Pro Leu Pro Cys Pro Lys Thr Gly Gly
100 105

PCT/US00/05881 WO 00/55173

427

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<210> 478
<211> 282
<212> PRT
<213> Homo sapiens
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<222> (281)
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Arg Glu Leu Gly Gly Thr Leu Leu Ser Ala Ile Glu Val Glu Gly Ala
1 . 5
Lys Met Gln Ser Asn Lys Thr Phe Asn Leu Glu Lys Gln Asn His Thr
Pro Arg Lys His His Gln His His Gln Gln Gln His His Gln Gln
                           40
Gln Gln Gln Pro Pro Pro Pro Pro Ile Pro Ala Asn Gly Gln Gln
Ala Ser Ser Gln Asn Glu Gly Leu Thr Ile Asp Leu Lys Asn Phe Arg
Lys Pro Gly Glu Lys Thr Phe Thr Gln Arg Ser Arg Leu Phe Val Gly
Asn Leu Pro Pro Asp Ile Thr Glu Glu Glu Met Arg Lys Leu Phe Glu
           100
                              105
Lys Tyr Gly Lys Ala Gly Glu Val Phe Ile His Lys Asp Lys Gly Phe
                           120
Gly Phe Ile Arg Leu Glu Thr Arg Thr Leu Ala Glu Ile Ala Lys Val
Glu Leu Asp Asn Met Pro Leu Arg Gly Lys Gln Leu Arg Val Arg Phe
145
Ala Cys His Ser Ala Ser Leu Thr Val Arg Asn Leu Pro Gln Tyr Val
Ser Asn Glu Leu Leu Glu Glu Ala Phe Ser Val Phe Gly Gln Val Glu
Arg Ala Val Val Ile Val Asp Asp Arg Gly Arg Pro Ser Gly Lys Gly
                           200
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WO 00/55173

Ile Val Glu Phe Ser Gly Lys Pro Ala Ala Arg Lys Ala Leu Asp Arg

428

PCT/US00/05881

215 Cys Ser Glu Gly Ser Phe Leu Leu Thr Thr Phe Pro Arg Pro Val Thr 230 235 Val Glu Pro Met Asp Gln Leu Asp Asp Glu Glu Gly Leu Pro Glu Lys 245 250 Leu Val Ile Lys Asn Gln Gln Phe His Lys Glu Arg Glu Gln Pro Pro 265 Arg Phe Ala Gln Pro Gly Ser Phe Xaa Val 275 <210> 479 <211> 289 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (206) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (215) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (218) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (285) <223> Xaa equals any of the naturally occurring L-amino acids <400> 479 Ala Val Pro Val Arg Asn Ser Arg Val Asp Pro Arg Val Arg Val Cys 5 Gly Pro Leu Ser Ala Pro Arg Gly Ser Arg Arg Pro Thr Val Pro Gly 20 25

Thr Pro Ala Cys Leu Ala Arg Pro Ala Ala Gln Gly Phe Ser Ala Ala

		35					40					45			
Leu	Pro 50	Val	Arg	Trp	Thr	Gly 55	Arg	Arg	Ala	Gly	Pro 60	Ser	Arg	Pro	Val
Pro 65	Ile	Gly	Thr	Pro	Ser 70	Arg	Ala	Ala	Asp	Pro 75	Ser	Gln	Gly	Glu	Met 80
Ser	Ala	Asp	Ala	Ala 85	Ala	Gly	Ala	Pro	Leu 90	Pro	Arg	Leu	Cys	Cys 95	Leu
Glu	Lys	Gly	Pro 100	Asn	Gly	Tyr	Gly	Phe 105	His	Leu	His	Gly	Glu 110	Lys	Gly
Lys	Leu	Gly 115	Gln	Tyr	Ile	Arg	Leu 120	Val	Glu	Pro	Gly	Ser 125	Pro	Ala	Glu
Lys	Ala 130	Gly	Leu	Leu	Ala	Gly 135	Asp	Arg	Leu	Val	Glu 140	Val	Asn	Gly	Glu
Asn 145	Val	Glu	Lys	Glu	Thr 150	His	Gln	Gln	Val	Val 155	Ser	Arg	Ile	Arg	Ala 160
Ala	Leu	Asn	Ala	Val 165	Arg	Leu	Leu	Val	Val 170	Asp	Pro	Glu	Thr	Asp 175	Glu
Gln	Leu	Gln	Lys 180	Leu	Gly	Val	Gln	Val 185	Arg	Glu	Glu	Leu	Leu 190	Arg	Ala
Gln	Glu	Ala 195	Pro	Gly	Gln	Ala	Glu 200	Pro	Pro	Ala	Ala	Ala 205	Xaa	Val	Gln
Gly	Ala 210	Gly	Asn	Glu	Asn	Xaa 215	Pro	Arg	Xaa	Ala	Asp ⁻ 220	Lys	Ser	His	Pro
Glu 225	Gln	Arg	Glu	Leu	Arg 230	Pro	Arg	Leu	Cys	Thr 235	Met	Lys	Lys	Gly	Pro 240
Ser	Gly	Tyr	Gly	Phe 245	Asn	Leu	His	Ser	Asp 250	Lys	Ser	Lys	Pro	Gly 255	Gln
Phe	Ile	Arg	Ser 260	Val	Asp	Pro	Asp	Ser 265	Pro	Ala	Glu	Ala	Ser 270	Gly	Leu
Arg	Ala	Gln 275	Asp	Arg	Ile	Val	Glu 280	Val	Met	Leu	Leu	Xaa 285	Ser	Leu	Pro

Ile

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<210> 480
<211> 44
<212> PRT ·
<213> Homo sapiens
<400> 480
Gly Ser Thr His Ala Ser Gly Arg Asn Glu Gly Pro Pro Ala Lys Thr
Lys Ser Trp Val Gly Pro Thr Leu His Phe His Arg Lys Ser Glu His
Leu Val Gly Leu Lys Val Leu Cys Cys Phe Arg Leu
         35
<210> 481
<211> 124
<212> PRT
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Ser Ile Xaa His Xaa Arg Lys Xaa Xaa Xaa Thr Val Arg Ser Asp Ser
                  5
                                     10
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431

Arg Val Asp Pro Arg Ser Asp Asp Phe Thr Pro Leu Glu Ile Leu Trp Thr Phe Ser Ile Tyr Leu Glu Ser Val Ala Ile Leu Pro Gln Leu Phe 40 Met Val Ser Lys Thr Gly Glu Ala Glu Thr Ile Thr Ser His Tyr Leu Phe Ala Leu Gly Val Tyr Arg Thr Leu Tyr Leu Phe Asn Trp Ile Trp 75 Arg Tyr His Phe Glu Gly Phe Phe Asp Leu Ile Ala Ile Val Ala Gly Leu Val Gln Thr Val Leu Tyr Cys Asp Phe Phe Tyr Leu Tyr Ile Thr 100 105 Lys Val Leu Lys Gly Lys Lys Leu Ser Leu Pro Ala 120 <210> 482 <211> 131 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (122) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (124) <223> Xaa equals any of the naturally occurring L-amino acids

<220> <221> SITE <222> (127) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (131) <223> Xaa equals any of the naturally occurring L-amino acids <400> 482 Cys Ser Ser Arg Gly Ala His His Ser His Cys Asp Arg Leu Pro His

10 Ser Pro Trp Pro Gly Leu Arg Glu Val Glu Leu Leu Ala Ser Val His 20 25 Thr Glu Gln Met Glu Glu Glu Leu Ala Leu Gly Pro Arg Gly Gln Gly 40 Gly Ala Ser Leu Ala Gly Arg Asp Gly Arg Ser Ala Gly Ala Gly Ser Tyr Gly Ala Leu Ala Asn Ser Ala Trp Gly Gly Pro Arg Lys Val Ala 75 70 Ser Ala Ser Ala Ala Ala Ser Thr Leu Ser Glu Pro Pro Arg Arg Thr 90 Gln Glu Ser Arg Thr Arg Thr Arg Ala Leu Gly Leu Pro Thr Leu Pro 105 Met Glu Lys Leu Ala Ala Ser Asn Arg Xaa Pro Xaa Gly Leu Xaa Gly 120 Pro Gly Xaa 130 <210> 483 <211> 221 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (168) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (174) <223> Xaa equals any of the naturally occurring L-amino acids <400> 483 Lys Lys Pro Pro Ile Thr His Pro Ser Thr Pro Ala Glu Glu Thr Tyr , 5 Asn Leu Gly Arg Gln Val Leu Pro Leu Ser Ala Val Thr Tyr Phe Gln 20 Lys Ser Gly Pro Gly Leu Leu Pro Ala Pro Ala Thr Gln Ser Ala Ser

WO 00/55173

<222> (54)

433

PCT/US00/05881

35 40 45 Val Ala Gly Thr Leu Gln Asn Ser Leu Cys Ser Gln Val Thr Lys Lys 55 Lys Arg Ala Asn Met Leu Val Leu Leu Ala Gly Ile Phe Val Val His 75 70 Ile Ala Thr Val Ile Met Leu Phe Val Ser Thr Ile Ala Asn Val Trp 90 Leu Val Ser Asn Thr Val Asp Ala Ser Val Gly Leu Trp Lys Asn Cys 105 100 Thr Asn Ile Ser Cys Ser Asp Ser Leu Ser Tyr Ala Ser Glu Asp Ala 120 Leu Lys Thr Val Gln Ala Phe Met Ile Leu Ser Ile Ile Phe Cys Val 135 Ile Ala Leu Leu Val Phe Val Phe Gln Leu Phe Thr Met Glu Lys Gly 145 150 155 Asn Arg Phe Phe Leu Ser Gly Kaa Thr Thr Leu Val Cys Kaa Leu Cys 165 170 Ile Leu Val Gly Cys Pro Ser Thr Leu Val Ile Met Arg Ile Val Met 180 185 Glu Arg Ile Cys Thr Thr Ala Ile Pro Thr Ser Trp Ala Gly Ser Ala 195 200 Ser Ala Ser Ala Ser Ser Ser Ala Phe Ser Ile Trp Ser 215 <210> 484 <211> 382 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (22) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE

<223> Xaa equals any of the naturally occurring L-amino acids

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<222> (358)
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Thr Lys Leu Trp Thr Leu Val Ser Asn Pro Asp Thr Asp Ala Leu Ile
                                     10
Cys Trp Ser Pro Ser Xaa Asn Ser Phe His Val Phe Asp Gln Gly Gln
                                 25
Phe Ala Lys Glu Val Leu Pro Lys Tyr Phe Lys His Asn Asn Met Ala
                                                 45
         35
                             40
Ser Phe Val Arg Gln Xaa Asn Met Tyr Gly Phe Arg Lys Val Val His
Ile Glu Gln Gly Xaa Leu Val Lys Pro Glu Arg Asp Asp Thr Glu Phe
                     70
                                         75
Gln His Pro Cys Phe Leu Arg Gly Gln Glu Gln Leu Leu Glu Asn Ile
                 85
                                     90
Lys Arg Lys Val Thr Ser Val Ser Thr Leu Lys Ser Glu Asp Ile Lys
                                105
Ile Arg Gln Asp Ser Val Thr Lys Leu Leu Thr Asp Val Gln Leu Met
                                                125
        115
                            120
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Lys	Gly 130	Lys	Gln	Glu	Cys	Met 135	Asp	Ser	Lys	Leu	Leu 140	Ala	Met	Lys	His
Glu 145	Asn	Glu	Ala	Leu	Trp 150	Arg	Glu	Val	Ala	Ser 155	Leu	Arg	Gln	Lys	His 160
Ala	Gln	Gln	Gln	Lys 165	Val	Val	Asn	Lys	Leu 170	Ile	Gln	Phe	Leu	Ile 175	Ser
Leu	Val	Gln	Ser 180	Asn	Arg	Ile	Leu	Gly 185	Val	Lys	Arg	Lys	Ile 190	Pro	Leu
Met	Leu	Asn 195	Asp	Ser	Gly	Ser	Ala 200	His	Ser	Met	Pro	Lys 205	Tyr	Ser	Arg
Gln	Phe 210	Ser	Leu	Glu	His	Val 215	His	Gly	Ser	Gly	Pro 220	туг	Ser	Ala	Pro
Ser 225	Pro	Ala	Tyr	Ser	Ser 230	Ser	Ser	Leu	Tyr	Ala 235	Pro	Asp	Ala	Val	Ala 240
Ser	Ser	Gly	Pro	11e 245	Ile	Ser	Asp	Ile	Thr 250	Glu	Leu	Ala	Pro	Ala 255	Ser
Pro	Met	Ala	Ser 260	Pro	Gly	Gly	Ser	Ile 265	Asp	Glu	Arg	Pro	Leu 270	Ser	Ser
Ser	Pro	Leu 275	Val	Arg	Val	Lys	Glu 280	Glu	Pro	Pro	Ser	Pro 285	Pro	Xaa	Ser
Pro	Arg 290	Val	Glu	Glu	Ala	Ser 295	Pro	Gly	Xaa	Pro	Ser 300	Ser	Val	Asp	Thr
Leu 305	Leu	Ser	Pro	Thr	Ala 310	Leu	Ile	Asp	Ser	11e 315	Leu	Arg	Glu	Ser	Glu 320
Pro	Ala	Pro	Xaa	Ser 325	Val	Thr	Ala	Leu	Thr 330	Asp	Ala	Arg	Gly	His 335	Thr
Asp	Thr	Glu	Gly 340	Arg	Pro	Pro	Ser	Pro 345	Pro	Pro	Thr	Ser	Thr 350	Pro	Glu
Lys	Cys	Leu 355	Ser	Val	Xaa	Ala	Trp 360	Thr	Arg	Met	Ser	Ser 365	Val	Thr	Thr
Trp	Met 370	Leu	Trp	Thr	Pro	Thr 375	Trp	Ile	Thr	Cys	Arg 380	Pro	Суѕ		

436

<211> 416 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (399) <223> Xaa equals any of the naturally occurring L-amino acids <400> 485 Pro Ser Val Ala Asn Val Gly Ser His Cys Asp Leu Ser Leu Lys Ile Pro Glu Ile Ser Ile Gln Asp Met Thr Ala Gln Val Thr Ser Pro Ser . 20 25 Gly Lys Thr His Glu Ala Glu Ile Val Glu Gly Glu Asn His Thr Tyr Cys Ile Arg Phe Val Pro Ala Glu Met Gly Thr His Thr Val Ser Val Lys Tyr Lys Gly Gln His Val Pro Gly Ser Pro Phe Gln Phe Thr Val Gly Pro Leu Gly Glu Gly Gly Ala His Lys Val Arg Ala Gly Gly Pro Gly Leu Glu Arg Ala Glu Ala Gly Val Pro Ala Glu Phe Ser Ile Trp 105 Thr Arg Glu Ala Gly Ala Gly Gly Leu Ala Ile Ala Val Glu Gly Pro Ser Lys Ala Glu Ile Ser Phe Glu Asp Arg Lys Asp Gly Ser Cys Gly Val Ala Tyr Val Val Gln Glu Pro Gly Asp Tyr Glu Val Ser Val Lys 145 150 155 Phe Asn Glu Glu His Ile Pro Asp Ser Pro Phe Val Val Pro Val Ala 165 Ser Pro Ser Gly Asp Ala Arg Arg Leu Thr Val Ser Ser Leu Gln Glu 185 Ser Gly Leu Lys Val Asn Gln Pro Ala Ser Phe Ala Val Ser Leu Asn 200 Gly Ala Lys Gly Ala Ile Asp Ala Lys Val His Ser Pro Ser Gly Ala

215

220

Leu 225	Glu	Glu	Cys	Tyr	Val 230	Thr	Glu	Ile	Asp	235	Asp	гÀг	TYT	Ala	240
Arg	Phe	Ile	Pro	Arg 245	Glu	Asn	Gly	Val	Туг 250	Leu	Ile	Asp	Val	Lys 255	Phe
Asn	Gly	Thr	His 260	Ile	Pro	Gly	Ser	Pro 265	Phe	Lys	Ile	Arg	Val 270	Gly	Glu
Pro	Gly	His 275	Gly	Gly	Asp	Pro	Gly 280	Leu	Val	Ser	Ala	Туг 285	Gly	Ala	Gly
Leu	Glu 290	Gly	Gly	Val	Thr	Gly 295	Asn	Pro	Ala	Glu	Phe 300	Val	Val	Asn	Thr
Ser 305	Asn	Ala	Gly	Ala	Gly 310	Ala	Leu	Ser	Val	Thr 315	Ile	Asp	Gly	Pro	Ser 320
Lys	Val	Lys	Met	Asp 325	Cys	Gln	Glu	Cys	Pro 330	Glu	Gly	Tyr	Arg	Val 335	Thr
Tyr	Thr	Pro	Met 340	Ala	Pro	Gly	Ser	туг 345	Leu	Ile	Ser	Ile	Lys 350	Tyr	Gly
Gly	Pro	Tyr 355	His	Ile	Gly	Gly	Ser 360	Pro	Phe	Lys	Ala	Lys 365	Val	Thr	Gly
Pro	Arg 370	Leu	Val	Ser	Asn	His 375	Ser	Leu	His	Glu	Thr 380	Ser	Ser	Val	Phe
Val 385	Asp	Ser	Leu	Thr	Lys 390	Ala	Thr	Cys	Ala	Pro 395	Gln	His	Gly	Xaa	Prc 400
Gly	Pro	Gly	Pro	Ala 405	Asp	Ala	Ser	Lys	Val 410	Val	Ala	Lys	Gly	Trp 415	Gly

<210> 486

<211> 46

<212> PRT

<213> Homo sapiens

405

<400> 486

Phe Val Thr Ser Gly Lys Ile Ser Leu Tyr Val Tyr Ile Leu Thr Ile 10 5

Arg Leu Asp Thr Asn Lys Ala Thr Leu Leu Thr Ala Ser Gly Glu Leu
20 25 30

Ile Leu Phe Leu Ile Phe Phe Asn Lys Asp Ile Leu Arg Tyr 35 40 45

<210> 487

<211> 162

<212> PRT

<213> Homo sapiens

<400> 487

Leu Gly Val Ala Leu Gly Ala Val Pro Lys Leu His Leu Gly Val Leu

1 10 15

Val Ser Thr Gly Leu Arg Thr Ala Val Gly Ser Pro Arg Leu Pro Pro 20 25 30

Thr Ala Leu Gly Ala Ala Tyr Gly Thr Ala Lys Ser Gly Thr Gly Ile 35 40 45

Ala Ala Met Ser Val Met Arg Pro Glu Gln Ile Met Lys Ser Ile Ile
50 60

Pro Val Val Met Ala Gly Ile Ile Ala Ile Tyr Gly Leu Val Val Ala 65 70 75 80

Val Leu Ile Ala Asn Ser Leu Asn Asp Asp Ile Ser Leu Tyr Lys Ser 85 90 95

Phe Leu Gln Leu Gly Ala Gly Leu Ser Val Gly Leu Ser Gly Leu Ala 100 105 110

Ala Gly Phe Ala Ile Gly Ile Val Gly Asp Ala Gly Val Arg Gly Thr
115 120 125

Ala Gln Gln Pro Arg Leu Phe Val Gly Met Ile Leu Ile Leu Ile Phe 130 135 140

Ala Glu Val Leu Gly Leu Tyr Gly Leu Ile Val Ala Leu Ile Leu Ser 145 150 155 160

Thr Lys

<210> 488

<211> 114

PCT/US00/05881

<212> PRT <213> Homo sapiens <220> <221> SITE <222> (95) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (111) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (113) <223> Xaa equals any of the naturally occurring L-amino acids <400> 488 Gln Ala Leu Arg Pro Gly Ser Phe Arg Gly Thr Gly Arg Lys Arg Glu 10 Arg Glu Arg Glu Arg Met Ser Leu Ser Asp Trp His Leu Ala Val Lys 20 Leu Ala Asp Gln Pro Leu Ala Pro Lys Ser Ile Leu Gln Leu Pro Glu Ser Glu Leu Gly Glu Tyr Ser Leu Gly Gly Tyr Ser Ile Ser Phe Leu Lys Gln Leu Ile Ala Gly Lys Leu Gln Glu Ser Val Pro Asp Pro Glu 70 Leu Ile Asp Leu Ile Tyr Cys Gly Arg Lys Leu Lys Asp Asp Xaa Thr

Leu Thr Ser Thr Val Phe Asn Leu Ala Pro His Pro Cys Ser Xaa Glu
100 105 110

Xaa Leu

<210> 489

<211> 149

<212> PRT

<213> Homo sapiens

<220>

440

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<400> 489
Ser Thr His Ala Ser Glu Asp Val Leu Ala Ala Pro Ser Gly Cys Arg
Ala Ser Arg Pro Pro Thr Ser Gly Arg Glu Gln Phe Trp Ala Arg Gly
             20
                                25
Leu Ala Ala Asp Met Thr Lys Gly Leu Val Leu Gly Ile Tyr Ser
                            40
Lys Asp Lys Glu Asp Asp Val Pro Gln Phe Thr Ser Ala Gly Glu Asn
                        55
Phe Asp Lys Leu Val Ser Gly Lys Leu Arg Glu Ile Leu Asn Ile Ser
                    70
Gly Pro Pro Leu Lys Ala Gly Lys Thr Arg Thr Phe Tyr Gly Leu His
                85
                                    90
Glu Asp Phe Pro Ser Val Val Val Gly Leu Gly Arg Lys Ala Ala
        100
                    105
Gly Val Asp Asp Gln Glu Asn Trp Xaa Glu Gly Lys Glu Asn Ile Arg
                           120
       115
Val Ala Met Gln Arg Gly Ala Gly Arg Phe Gln Asp Leu Xaa Ile Ser
                       135
Ser Val Glu Gly Gly
145
<210> 490
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<211> 527
<212> PRT
<213> Homo sapiens

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<400	<400> 490 Arg Arg Arg Ser Arg Gly Leu Ile Pro Gly Arg Ala Pro Gly Arg Arg														
Arg 1	Arg	Arg	Ser	Arg 5	Gly	Leu	Ile	Pro	Gly 10	Arg	Ala	Pro	Gly	Arg 15	Arg
Arg	Pro	Arg	Ala 20	His	Glu	Val	Ala	Arg 25	Ala	Pro	Pro	Pro	Ile 30	Ala	Met
Asp	Arg	Met 35	Lys	Lys	Ile	Lys	Arg 40	Gln	Leu	Ser	Met	Thr 45	Leu	Arg	Gly
Gly	Arg 50	Gly	Ile	Asp	Lys	Thr 55	Asn	Gly	Ala	Pro	Glu 60	Gln	Ile	Gly	Leu
Asp 65	Glu	Ser	Gly	Gly	Gly 70	Gly	Gly	Ser	Asp	Pro 75	Gly	Glu	Ala	Pro	Thr 80
Arg	Ala	Ala	Pro	Gly 85	Glu	Leu	Arg	Ser	Ala 90	Arg	Gly	Pro	Leu	Ser 95	Ser
Ala	Pro	Glu	Ile 100	Val	His	Glu	Asp	Leu 105	Lys	Met	Gly	Ser	Asp 110	Gly	Glu
Ser	Asp	Gln 115	Ala	Ser	Ala	Thr	Ser 120	Ser	Asp	Glu	Val	Gln 125	Ser	Pro	Val
Arg	Val 130	Arg	Met	Arg	Asn	His 135	Pro	Pro	Arg	Lys	Ile 140	Ser	Thr	Glu	Asp
Ile 145	Asn	Lys	Arg	Leu	Ser 150	Leu	Pro	Ala	Asp	Ile 155	Arg	Leu	Pro	Glu	Gly 160
Tyr	Leu	Glu	Lys	Leu 165	Thr	Leu	Asn	Ser	Pro 170	Ile	Phe	Asp	Lys	Pro 175	Leu
Ser	Arg	Arg	Leu 180	Arg	Arg	Val	Ser	Leu 185	Ser	Glu	Ile	Gly	Phe 190	Gly	Lys
Leu	Glu	Thr 195	Tyr	Ile	Lys	Leu	Asp 200	Lys	Leu	Gly	Glu	Gly 205	Thr	туr	Ala
Thr	Val 210	Tyr	Lys	Gly	Lys	Ser 215	Lys	Leu	Thr	Asp	Asn 220	Leu	Val	Ala	Leu
Lys 225	Glu	Ile	Arg	Leu	Glu 230	His	Glu	Glu	Gly	Ala 235	Pro	Cys	Thr	Ala	Ile 240

Arg Glu Val Ser Leu Leu Lys Asp Leu Lys His Ala Asn Ile Val Thr

Leu His Asp Ile Ile His Thr Glu Lys Ser Leu Thr Leu Val Phe Glu

PCT/US00/05881

			260					265					270		
туг	Leu	Asp 275	Lys	Asp	Leu	Lys	Gln 280	Tyr	Leu	Asp	Asp	Cys 285	Gly	Asn	Ile
Ile	Asn 290	Met	His	Asn	Val	Lys 295	Leu	Phe	Leu	Phe	Gln 300	Leu	Leu	Arg	Gly
Leu 305	Ala	туг	Cys	His	Arg 310	Xaa	Lys	Val	Leu	His 315	Arg	Asp	Leu	Lys	Pro 320
Gln	Asn	Leu	Leu	Ile 325	Asn	Glu	Arg	Gly	Glu 330	Leu	Lys	Leu	Ala	Asp 335	Phe
Gly	Leu	Ala	Arg 340	Ala	Lys	Ser	Ile	Pro 345	Thr	Lys	Thr	Tyr	Ser 350	Asn	Glu
Val	Val	Thr 355	Leu	Trp	Tyr	Arg	Pro 360	Pro	Asp	Ile	Leu	Leu 365	Gly	Ser	Thr
Asp	Tyr 370	Ser	Thr	Gln	Ile	Asp 375	Met	Trp	Gly	Val	Gly 380	Cys	Ile	Phe	Tyr
Glu 385	Met	Ala	Thr	Gly	Arg 390	Pro	Leu	Phe	Pro	Gly 395	Ser	Thr	Val	Glu	Glu 400
Gln	Leu	His	Phe	Ile 405	Phe	Arg	Ile	Leu	Gly 410	Thr	Pro	Thr	Glu	Glu 415	Thr
Trp	Pro	Gly	11e 420	Leu	Ser	Asn	Glu	Glu 425	Phe	Lys	Thr	Tyr	Asn 430	Tyr	Pro
Lys	Tyr	Arg 435	Ala	Glu	Ala	Leu	Leu 440	Ser	His	Ala	Pro	Arg 445	Leu	Asp	Ser
Asp	Gly 450	Ala	Asp	Leu	Leu	Thr 455	ГÀ̀	Leu	Leu	Gln	Phe 460	Glu	Gly	Arg	Asn
Arg 465	Ile	Ser	Ala	Glu	Asp 470	Ala	Met	Lys	His	Pro 475	Phe	Phe	Leu	Ser	Leu 480
Gly	Glu	Arg	Ile	His 485	Lys	Leu	Pro	Asp	Thr 490	Thr	Ser	Ile	Phe	Ala 495	Leu
Lys	Glu	Ile	Gln 500	Leu	Gln	Lys	Glu	Ala 505	Ser	Leu	Arg	Ser	Ser 510	Ser	Met
Pro	Asp	Ser 515	Gly	Arg	Pro	Ala	Phe 520	Arg	Val	Val	Asp	Thr 525	Glu	Phe	

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443
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<210> 491 <211> 125 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (125) <223> Xaa equals any of the naturally occurring L-amino acids Cys Thr Arg Ala His Pro Lys Asn Leu Val Glu Lys Gly Ile Leu Thr Thr Glu Lys Gln Asn Phe Leu Leu Phe Asp Met Thr Thr His Pro Val 25 Thr Asn Thr Thr Glu Lys Gln Arg Leu Val Lys Lys Leu Gln Asp Ser 35 40 Val Leu Glu Arg Trp Val Asn Asp Pro Gln Arg Met Asp Lys Arg Thr 55 Leu Ala Leu Leu Val Leu Ala His Ser Ser Asp Val Leu Glu Asn Val 65 70 75 Phe Ser Ser Leu Thr Asp Asp Lys Tyr Asp Val Ala Met Asn Arg Ala 90 Lys Asp Leu Val Glu Leu Asp Pro Glu Val Glu Gly Thr Lys Pro Ser 105 100 Ala Thr Glu Met Ile Trp Ala Val Leu Ala Ala Phe Xaa 115 120 <210> 492 <211> 53 <212> PRT <213> Homo sapiens <220>

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<222> (49)

<221> SITE <222> (3)

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<400> 492
Val Ser Xaa Ser Ile Leu Ala Leu Leu Phe Asn Thr Asp Ala Leu Phe
Ser Arg Val Tyr Glu Ser Leu Ser Asp Asn His Gly Leu Gln Glu Gln
             20
                                 25
Thr Val Glu Lys Leu Phe Phe Gln Trp Lys Ser Trp Val Gln Glu Met
                             40
Xaa Gly Xaa Leu Lys
    50
<210> 493
<211> 82
<212> PRT
<213> Homo sapiens
<220>
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<222> (60)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
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<222> (67)
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<400> 493 Pro Gly Phe Phe Gln Met Leu Val His Thr Tyr Ser Ser Met Asp Arg His Asp Gly Val Pro Ser His Ser Ser Arg Leu Ser Gln Leu Gly Ser Val Ser Gln Gly Pro Tyr Ser Ser Ala Pro Pro Leu Ser His Thr 40 Pro Ser Ser Asp Phe Gln Pro Pro Tyr Phe Pro Xaa Pro Tyr Gln Pro 55 Leu Pro Xaa Xaa Gln Ser Gln Asp Pro Tyr Ser His Val Xaa Xaa Pro 70 Tyr Pro <210> 494 <211> 290 <212> PRT <213> Homo sapiens <400> 494 Tyr Lys Asp Trp Leu Thr Lys Met Ser Gly Lys His Asp Val Gly Ala 10 Tyr Met Leu Met Tyr Lys Gly Ala Asn Arg Thr Glu Thr Val Thr Ser Phe Arg Lys Arg Glu Ser Lys Val Pro Ala Asp Leu Leu Lys Arg Ala Phe Val Arg Met Ser Thr Ser Pro Glu Ala Phe Leu Ala Leu Arg Ser 55 His Phe Ala Ser Ser His Ala Leu Ile Cys Ile Ser His Trp Ile Leu 65 Gly Ile Gly Asp Arg His Leu Asn Asn Phe Met Val Ala Met Glu Thr 90 Gly Gly Val Ile Gly Ile Asp Phe Gly His Ala Phe Gly Ser Ala Thr 105

Gln Phe Leu Pro Val Pro Glu Leu Met Pro Phe Arg Leu Thr Arg Gln

120

Phe Ile Asn Leu Met Leu Pro Met Lys Glu Thr Gly Leu Met Tyr Ser 135 Ile Met Val His Ala Leu Arg Ala Phe Arg Ser Asp Pro Gly Leu Leu 155 150 Thr Asn Thr Met Asp Val Phe Val Lys Glu Pro Ser Phe Asp Trp Lys 170 Asn Phe Glu Gln Lys Met Leu Lys Lys Gly Gly Ser Trp Ile Gln Glu Ile Asn Val Ala Glu Lys Asn Trp Tyr Pro Arg Gln Lys Ile Cys Tyr 200 Ala Lys Arg Lys Leu Ala Gly Ala Asn Pro Ala Val Ile Thr Cys Asp Glu Leu Leu Gly His Glu Lys Ala Pro Ala Phe Arg Asp Tyr Val Ala Val Ala Arg Gly Ser Lys Asp His Asn Ile Arg Ala Gln Glu Pro 245 Glu Ser Gly Leu Ser Glu Glu Thr Gln Val Lys Cys Leu Met Asp Gln Ala Thr Asp Pro Asn Ile Leu Gly Arg Thr Trp Glu Gly Trp Glu Pro 280 Trp Met 290 <210> 495 <211> 156 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (148) <223> Xaa equals any of the naturally occurring L-amino acids. Cys Gln Ser His Pro Leu Pro Gly Gly Pro Ala Cys Pro Cys Leu Ala Cys His Ile Thr Leu Leu Phe Gly Arg Pro Trp Leu Ile Lys Glu Val

447

25 20 Leu Val Val Ser Gln Ala Lys Trp Asn Leu Glu Thr Val Lys Lys Val 40 45 Gln Ile Thr Leu Asn Cys Ile Gln Glu Val His Phe Phe Pro Ile Val 55 Arg Gly Ser Trp Ser Leu Arg Asp Ala Arg Leu Glu Ser Asp Tyr Ile Ile Ile Gln Asn Gly Asn Ser Gln Gly Asn Ala Phe Phe His Phe Ile 90 95 85 Arg Phe Phe Tyr Pro His Cys Thr Pro Ser Pro Ser Pro Leu Pro Ile 105 Trp Met Ala Ser Gln Lys Leu Gly Pro Ser Pro Pro Cys Leu Gly Gly 115 120 125 Gly Gln Ser Pro Leu Thr Ala Glu Ala Ala Leu Leu Ser Ser Ala Val 130 135 Leu Pro Leu Xaa Lys Cys Leu Gln Arg Val Met Ser 150 <210> 496 <211> 251 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (42) <223> Xaa equals any of the naturally occurring L-amino acids <400> 496 Glu Glu Leu Leu Arg Ala Gln Glu Ala Pro Gly Gln Ala Glu Pro Pro Ala Ala Ala Glu Val Gln Gly Ala Gly Asn Glu Asn Glu Pro Arg Glu Ala Asp Lys Ser His Pro Glu Gln Arg Xaa Leu Arg Pro Arg Leu Cys Thr Met Lys Lys Gly Pro Ser Gly Tyr Gly Phe Asn Leu His Ser Asp 55

Lys 65	Ser	Lys	Pro	Gly	Gln 70	Phe	Ile	Arg	Ser	Val 75	Asp	Pro	Asp	Ser	Pro 80
Ala	Glu	Ala	Ser	Gly 85	Leu	Arg	Ala	Gln	Asp 90	Arg	Ile	Val	Glu	Val 95	Asr
Gly	Val	Cys	Met 100	Glu	Gly	Lys	Gln	His 105		Asp	Val	Val	Ser 110	Ala	Ile
Arg	Ala	Gly 115	Gly	Asp	Glu	Thr	Lys 120	Leu	Leu	Val	Val	Asp 125	Arg	Glu	Thr
Asp	Glu 130	Phe	Phe	Lys	Lys	Cys 135	Arg	Val	Ile	Pro	Ser 140	Gln	Glu	His	Leu
Asn 145	Gly	Pro	Leu	Pro	Val 150	Pro	Phe	Thr	Asn	Gly 155	Glu	Ile	Gln	Lys	Glu 160
Asn	Ser	Arg	Glu	Ala 165	Leu	Ala	Glu	Ala	Ala 170	Leu	Glu	Ser	Pro	Arg 175	Pro
Ala	Leu	Val	Arg 180	Ser	Ala	Ser	Ser	Asp 185	Thr	Ser	Glu	Glu	Leu 190	Asn	Ser
Gln	Asp	Ser 195	Pro	Pro	Lys	Gln	Asp 200	Ser	Thr	Ala	Pro	Ser 205	Ser	Thr	Ser
Ser	Ser 210	Asp	Pro	Ile	Leu	Asp 215	Phe	Asn	Ile	Ser	Leu 220	Ala	Met	Ala	Lys
31u 225	Arg	Ala	His	Gln	Lys 230	Arg	Ser	Ser	Lys	Arg 235	Ala	Pro	Gln	Met	Asp 240
Prp	Ser	Lys	Lys	Asn 245	Glu	Leu	Phe	Ser	Asn 250	Leu					

<210> 497 <211> 48 <212> PRT <213> Homo sapiens

<400> 497

Asn Gly Ala Glu Ala Val Ser Thr Glu Ala Lys Met Thr Ala Phe Pro 1 5 10 15

Asp Trp Pro Trp Leu Phe His Thr Leu Cys Asp Pro Cys Pro Met Thr 20 25 30

Leu Trp Leu Thr Leu Pro Glu Ala Met Thr Thr Ala Ala Phe Cys His

449

35 40 45

<210> 498 <211> 373 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (337) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (372) <223> Xaa equals any of the naturally occurring L-amino acids Gly Thr Arg Gly Ser Arg Ala Ser Gly Val Cys Ala Arg Gly Cys Leu 10 Asp Ser Ala Gly Pro Trp Thr Met Ser Arg Ala Leu Arg Pro Pro Leu 25 Pro Pro Leu Cys Phe Phe Leu Leu Leu Leu Ala Ala Gly Ala Arg 40 35 45 Ala Gly Gly Tyr Glu Thr Cys Pro Thr Val Gln Pro Asn Met Leu Asn 55 Val His Leu Leu Pro His Thr His Asp Asp Val Gly Trp Leu Lys Thr 65 70 75 Val Asp Gln Tyr Phe Tyr Gly Ile Lys Asn Asp Ile Gln His Ala Gly Val Gln Tyr Ile Leu Asp Ser Val Ile Ser Ala Leu Leu Ala Asp Pro 105 Thr Arg Arg Phe Ile Tyr Val Glu Ile Ala Phe Phe Ser Arg Trp Trp 115 120 His Gln Gln Thr Asn Ala Thr Gln Glu Val Val Arg Asp Leu Val Arg 130 135

Gln Gly Arg Leu Glu Phe Ala Asn Gly Gly Trp Val Met Asn Asp Glu

450

145					150					155					160
Ala	Ala	Thr	His	Туг 165	Gly	Ala	Ile	Val	Asp 170	Gln	Met	Thr	Leu	Gly 175	Leu
Arg	Phe	Leu	Glu 180	Asp	Thr	Phe	Gly	Asn 185	Asp	Gly	Arg	Pro	Arg 190	Val	Ala
Trp	His	Ile 195	Asp	Pro	Phe	Gly	His 200	Ser	Arg	Glu	Gln	Ala 205	Ser	Leu	Phe
Ala	Gln 210	Met	Gly	Phe	Asp	Gly 215	Phe	Phe	Phe	Gly	Arg 220	Leu	Asp	Tyr	Gln
Asp 225	Lys	Trp	Val	Arg	Met 230	Gln	Lys	Leu	Glu	Met 235	Glu	Gln	Val	Trp	Arg 240
Ala	Ser	Thr	Ser	Leu 245	Lys	Pro	Pro	Thr	Ala 250	Asp	Leu	Phe	Thr	Gly 255	Val
Leu	Pro	Asn	Gly 260	Tyr	Asn	Pro	Pro	Arg 265	Asn	Leu	Суз	Trp	Asp 270	Val	Leu
Cys	Val	Asp 275	Gln	Pro	Leu	Val	Glu 280	Asp	Pro	Arg	Ser	Pro 285	Glu	Tyr	Asn
Ala	Lys 290	Glu	Leu	Val	Asp	Tyr 295	Phe	Leu	Asn	Val	Ala 300	Thr	Ala	Gln	Gly
Arg 305	Tyr	Tyr	Arg	Thr	Asn 310	His	Thr	Val	Met	Thr 315	Met	Gly	Ser	Asp	Phe 320
Gln	Tyr	Glu	Asn	Ala 325	Asn	Met	Trp	Phe	Lys 330	Asn	Leu	Asp	Lys	Leu 335	Ile
Xaa	Leu	Val	Asn 340	Ala	Gln	Gly	Lys	Arg 345	Lys	Gln	Cys	Pro	Cys 350	Ser	Leu
Leu	His	Pro 355	Arg	Leu	Leu	Pro	Leu 360	Gly	Ala	Glu	Gln	Gly 365	Gln	Pro	His

<210> 499

370

<211> 238

<212> PRT

<213> Homo sapiens

Leu Val Ser Xaa Thr

451

<400)> 49	9													
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Pro	Ala	Ala	Pro 20	Pro	Arg	Pro	Gly	Pro 25	Cys	Ala	Tyr	Ala	Ala 30	His	Gly
Arg	Gly	Ala 35	Leu	Ala	Glu	Ala	Ala 40	Arg	Arg	Cys	Leu	His 45	Asp	Ile	Ala
Leu	Ala 50	His	Arg	Ala	Ala	Thr 55	Ala	Ala	Arg	Pro	Pro 60	Ala	Pro	Pro	Pro
Ala 65	Pro	Gln	Pro	Pro	Ser 70	Pro	Thr	Pro	Ser	Pro 75	Pro	Arg	Pro	Thr	Leu 80
Ala	Arg	Glu	Asp	Asn 85	Glu	Glu	Asp	Glu	Asp 90	Glu	Pro	Thr	Glu	Thr 95	Glu
Thr	Ser	Gly	Glu 100	Gln	Leu	Gly	Ile	Ser 105	Asp	Asņ	Gly	Gly	Leu 110	Phe	Val
Met	Asp	Glu 115	Asp	Ala	Thr	Leu	Gln 120	Asp	Leu	Pro	Pro	Phe 125	Cys	Glu	Ser
Asp	Pro 130	Glu	Ser	Thr	Asp	Asp 135	Gly	Ser	Leu	Ser	Glu 140	Glu	Thr	Pro	Ala
Gly 145	Pro	Pro	Thr	Cys	Ser 150	Val	Pro	Pro	Ala	Ser 155	Ala	Leu	Pro	Thr	Gln 160
Gln	Tyr	Ala	Lys	Ser 165	Leu	Pro	Val	Ser	Val 170	Pro	Val	Trp	Gly	Phe 175	Lys
Glu	Lys	Arg	Thr 180	Glu	Ala	Arg	Ser	Ser 185	Asp	Glu	Glu	Asn	Gly 190	Pro	Pro

Arg Leu Asn Thr Ser Asp Phe Gln Lys Leu Lys Arg Lys Tyr
225 230 235

215

Ser Ser Pro Asp Leu Asp Arg Ile Ala Ala Ser Met Arg Ala Leu Val

Leu Arg Glu Ala Glu Asp Thr Gln Val Phe Gly Asp Leu Pro Arg Pro

200

<210> 500

210

195

<211> 198

<212> PRT

452

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<222> (94)
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                                    10
Ala Arg Ala Gly Asp Ala Gly Pro Ala Ala Arg Ser Arg Lys Gln Asn
Pro Gln Ser Pro Pro Cys Cys Cys Val Asp Asp Thr Trp Ala Gln Ala
Glu Val Gly Pro Val Thr Ser Cys Thr Gly Phe Val Glu Gly Ser Ser
     50
Arg Thr Gly Gly Met Gly Ser Ala Cys Ile Lys Val Thr Lys Tyr Phe
Leu Phe Leu Phe Asn Leu Ile Phe Phe Ile Leu Gly Ala Xaa Ile Leu
Gly Phe Gly Val Trp Ile Leu Ala Asp Lys Ser Ser Phe Ile Ser Val
           100
Leu Gln Thr Ser Ser Ser Leu Arg Met Gly Ala Tyr Val Phe Ile
Gly Val Gly Ala Val Thr Met Leu Met Gly Phe Leu Gly Cys Ile Gly
Ala Val Asn Glu Val Arg Cys Leu Leu Gly Leu Xaa Phe Ala Phe Leu
145
                   150
Leu Leu Ile Leu Ile Ala Gln Val Thr Ala Gly Ala Leu Phe Tyr Phe
                                   170
Asn Met Gly Lys Val Ser Pro Ser Leu Pro Pro Ser Ser Leu Gly Trp
           180
                               185
Thr Asn His Gly Gly Asp
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<210> 501
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<212> PRT
<213> Homo sapiens

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<223> Xaa equals any of the naturally occurring L-amino acids
<400> 501

Ser Ser Ala Ser Thr Asn Met Ser Arg Gly Ser Ser Ala Gly Phe Asp 1 5 10 15

Arg His Ile Thr Ile Phe Ser Pro Glu Gly Arg Leu Tyr Gln Val Glu 20 25 30

Tyr Ala Phe Lys Ala Ile Asn Gln Gly Gly Leu Thr Ser Val Ala Val 35 40 45

Arg Gly Lys Asp Cys Ala Val Ile Val Thr Gln Lys Lys Val Pro Asp 50 55 60

Lys Leu Leu Asp Ser Ser Thr Val Thr His Leu Phe Lys Ile Thr Glu
65 70 75 80

Asn Ile Gly Cys Val Met Thr Gly Met Thr Ala Asp Ser Arg Ser Gln 85 90 95

Val Gln Arg Ala Arg Tyr Glu Ala Ala Asn Trp Lys Tyr Lys Tyr Gly 100 105 110

Tyr Glu Ile Pro Val Asp Met Leu Cys Lys Arg Ile Ala Asp Ile Ser 115 120 125

Gln Val Tyr Thr Gln Asn Ala Glu Met Arg Pro Leu Gly Cys Cys Met 130 135 140

Ile Leu Ile Gly Ile Asp Glu Glu Gln Gly Pro Gln Val Tyr Lys Cys 145 150 155 160

Asp Pro Ala Gly Xaa Tyr Cys Gly Val 165

<210> 502

<211> 507

454

<212> PRT <213> Homo sapiens <220> <221> SITE <222> (10) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (361) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (461) <223> Xaa equals any of the naturally occurring L-amino acids <400> 502 Val Arg Gln Leu Cys Arg Pro Ala Glu Xaa Asp Ser Val Met Ala Glu Gln Val Ala Leu Ser Arg Thr Gln Val Cys Gly Ile Leu Arg Glu Glu 20 Leu Phe Gln Gly Asp Ala Phe His Gln Ser Asp Thr His Ile Phe Ile Ile Met Gly Ala Ser Gly Asp Leu Ala Lys Lys Lys Ile Tyr Pro Thr Ile Trp Trp Leu Phe Arg Asp Gly Leu Leu Pro Glu Asn Thr Phe Ile Val Gly Tyr Ala Arg Ser Arg Leu Thr Val Ala Asp Ile Arg Lys Gln Ser Glu Pro Phe Phe Lys Ala Thr Pro Glu Glu Lys Leu Lys Leu Glu 100 105 Asp Phe Phe Ala Arg Asn Ser Tyr Val Ala Gly Gln Tyr Asp Asp Ala Ala Ser Tyr Gln Arg Leu Asn Ser His Met Asn Ala Leu His Leu Gly 135 Ser Gln Ala Asn Arg Leu Phe Tyr Leu Ala Leu Pro Pro Thr Val Tyr 145 Glu Ala Val Thr Lys Asn Ile His Glu Ser Cys Met Ser Gln Ile Gly 165 170

	Trp	Asn	Arg	Ile 180	Ile	Val	Glu	Lys	Pro 185	Phe	Gly	Arg	Asp	Leu 190	Gln	Ser
	Ser	Asp	Arg 195	Leu	Ser	Asn	His	Ile 200	Ser	Ser	Leu	Phe	Arg 205	Glu	Asp	Gln
	Ile	Tyr 210	Arg	Ile	Asp	His	Tyr 215	Leu	Gly	Lys	Glu	Met 220	Val	Gln	Asn	Leu
	Met 225	Val	Leu	Arg	Phe	Ala 230	Asn	Arg	Ile	Phe	Gly 235	Pro	Ile	Trp	Asn	Arg 240
	Asp	Asn	Ile	Ala	Cys 245	Val	Ile	Leu	Thr	Phe 250	Lys	Glu	Pro	Phe	Gly 255	Thr
				Gly 260					265					270		
			275	His				280					285			
		290		Thr			295					300				
	305			Ile		310					315					320
				Asn	325					330					335	
,				Thr 340					345					350		
			355	Tyr				360					365			
		370		Gly			375					380				
	385			Asp		390					395					400
				Val	405					410					415	
				Lys 420					425					430		
	Leu	Asp	Leu 435	Thr	Tyr	Gly	Asn	Arg 440	Туг	Lys	Asn	Val	Lys 445	Leu	Pro	Asp

Ala Tyr Glu Arg Leu Ile Leu Asp Val Phe Cys Gly Xaa Gln Met His 455 Phe Val Arg Arg Thr Ser Ser Val Arg Pro Gly Val Phe Ser Pro His 475 470

Cys Cys Thr Arg Leu Ser Trp Arg Ser Pro Ser Pro Ser Pro Ile Phe 490 485

Met Ala Ala Glu Ala Pro Arg Arg Gln Thr Ser 505 500

<210> 503

<211> 260

<212> PRT

<213> Homo sapiens

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<222> (69)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 503

Gly Pro Glu Val Leu Pro Glu Pro Arg Val Pro Arg Glu Ala Leu Ala 1 5 10

Phe Ile Ile Arg Ser Phe Gly Gly Glu Val Ser Trp Asp Lys Ser Leu 25

Cys Ile Gly Ala Thr Tyr Asp Val Thr Asp Ser Arg Ile Thr His Gln 40

Ile Val Asp Arg Pro Gly Gln Gln Thr Ser Val Ile Gly Arg Cys Tyr 55

Val Gln Pro Gln Xaa Val Phe Asp Ser Val Asn Ala Arg Leu Leu

Pro Val Ala Glu Tyr Phe Ser Gly Val Gln Leu Pro Pro His Leu Ser 90

Pro Phe Val Thr Glu Lys Glu Gly Asp Tyr Val Pro Pro Glu Lys Leu 105 100

Lys Leu Leu Ala Leu Gln Arg Gly Glu Asp Pro Gly Asn Leu Asn Glu 120

Ser Glu Glu Glu Glu Glu Asp Asp Asn Asn Glu Gly Asp Gly Asp

130 135 140 Glu Glu Gly Glu Asn Glu Glu Glu Glu Glu Asp Ala Glu Ala Gly Ser 150 155 Glu Lys Glu Glu Glu Ala Arg Leu Ala Ala Leu Glu Glu Gln Arg Met 165 170 Glu Gly Lys Lys Pro Arg Val Met Ala Gly Thr Leu Lys Leu Glu Asp 185 Lys Gln Arg Leu Ala Gln Glu Glu Ser Glu Ala Lys Arg Leu Ala 195 200 Ile Met Met Lys Lys Arg Glu Lys Tyr Leu Tyr Gln Lys Ile Met 215 Phe Gly Lys Arg Arg Lys Ile Arg Glu Ala Asn Lys Leu Ala Glu Lys 230 235 Arg Lys Ala His Asp Glu Ala Val Arg Ser Glu Lys Lys Ala Lys Lys 245 Ala Arg Pro Glu 260 <210> 504 <211> 424 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (292) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (342) <223> Xaa equals any of the naturally occurring L-amino acids <400> 504 Leu Leu Gln Arg Cys Tyr Ala Phe Pro Gly His Arg Leu Ala His Ser 5 10 Gly Ser Asp Leu Ser Leu Leu Val Pro Glu Ile Glu Asp Met Tyr Ser 25

Ser Pro Tyr Leu Arg Pro Ser Glu Ser Pro Ile Thr Val Glu Val Asn

		35					40					45			
Cys	Thr 50	Asn	Pro	Gly	Thr	Arg 55	Tyr	Суѕ	Trp	Met	Ser 60	Thr	Gly	Leu	Туг
Ile 65	Pro	Gly	Arg	Gln	Ile 70	Ile	Glu	Val	Ser	Leu 75	Pro	Glu	Ala	Ala	Ala 80
Ser	Ala	Asp	Leu	Lys 85	Ile	Gln	Ile	Gly	Cys 90	His	Thr	Asp	Asp	Leu 95	Thr
Arg	Ala	Ser	Lys 100	Leu	Phe	Arg	Gly	Pro 105	Leu	Val	Ile	Asn	Arg 110	Cys	Cys
Leu	Asp	Lys 115	Pro	Thr	Lys	Ser	Ile 120	Thr	Cys	Leu	Trp	Gly 125	Gly	Leu	Leu
ryr	11e 130	Ile	Val	Pro	Gln	Asn 135	Ser	Lys	Leu	Gly	Ser 140	Val	Pro	Val	Thr
Val 145	Lys	Gly	Ala	Val	His 150	Ala	Pro	Tyr	Tyr	Lys 155	Leu	Gly	Glu	Thr	Thr 160
Leu	Glu	Glu	Trp	Lys 165	Arg	Arg	Ile	Gln	Glu 170	Asn	Pro	Gly	Pro	Trp 175	Gly
31u	Leu	Ala	Thr 180	Asp	Asn	Ile	Ile	Leu 185	Thr	Val	Pro	Thr	Ala 190	Asn	Leu
Arg	Thr	Leu 195	Glu	Asn	Pro	Glu	Pro 200	Leu	Leu	Arg	Leu	Trp 205	Asp	Glu	Val
Met	Gln 210	Ala	Val	Ala	Arg	Leu 215	Gly	Ala	Glu	Pro	Phe 220	Pro	Leu	Arg	Leu
Pro 225	Gln	Arg	Ile	Val	Ala 230	Asp	Val	Gln	Ile	Ser 235	Val	Gly	Trp	Met	His 240
Ala	Gly	Tyr	Pro	11e 245	Met	Суѕ	His		Glu 250		Val	Gln	Glu	Leu 255	
Asn	Glu	Lys	Leu 260	Ile	Arg	Thr	Lys	Gly 265	Leu	Trp	Gly	Pro	Val 270	His	Glu
Leu	Gly	Arg 275	Asn	Gln	Gln	Arg	Gln 280	Glu	Trp	Glu	Phe	Pro 285	Pro	His	Thr
Chr	Glu 290	Ala	Xaa	Cys	Asn	Leu 295	Trp	Cys	Val	Tyr	Val 300	His	Glu	Thr	Val
.611	Glv	Tle	Pro	Ara	Ser	Ara	Ala	Asn	Ile	Ala	Leu	Trp	Pro	Pro	Va1

PCT/US00/05881 WO 00/55173

459

310 315 320 305 Arg Glu Lys Arg Val Arg Ile Tyr Leu Ser Lys Gly Pro Asn Val Lys 325 330 Asn Trp Asn Ala Trp Xaa Ala Leu Glu Thr Tyr Leu Gln Leu Gln Glu 345 340 Ala Phe Gly Trp Glu Pro Phe Ile Arg Leu Phe Thr Glu Tyr Arg Asn 360 Gln Thr Asn Leu Pro Thr Glu Asn Val Asp Lys Met Asn Leu Trp Val 375 370 Lys Met Phe Ser His Gln Val Gln Lys Asn Leu Ala Pro Phe Glu 395 390 385 Ala Trp Ala Gly Pro Ser Arg Arg Lys Trp Leu Pro Ala Trp Pro Ile 410 405 Cys Leu Asn Gly Arg Lys Ile Leu 420 <210> 505 <211> 70 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (49) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (54) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (66) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (70) <223> Xaa equals any of the naturally occurring L-amino acids <400> 505

Leu His Gln Ser Leu Leu His Leu Glu Lys Thr Asn Glu Arg Lys Ser 1 5 10 Ile Phe Leu Ile His Tyr Pro Asn Asn Asn Arg Thr Pro Tyr Arg Asn 25 Tyr Tyr His Tyr Val Ser Lys His Tyr Ile Pro Ile Thr Tyr Pro Thr 40 Xaa Ser Ile Ile Asp Xaa Ile Ser Ile Pro Thr Met Ile Ser Ala Leu 55 Asn Xaa Gln Asn Lys Xaa <210> 506 <211> 434 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (69) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (135) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (363) <223> Xaa equals any of the naturally occurring L-amino acids Ser Thr His Ala Ser Ala His Ala Ser Val Ser Thr Ala Ala Ala Ala 10 Ala Leu Ala Ala Ala Val Lys Ala Lys His Leu Ala Ala Val Glu Glu Arg Lys Ile Lys Ser Leu Val Ala Leu Leu Val Glu Thr Gln Met 35 40 Lys Lys Leu Glu Ile Lys Leu Arg His Phe Glu Glu Leu Glu Thr Ile

55

Met Asp Arg Glu Xaa Glu Ala Leu Glu Tyr Gln Arg Gln Gln Leu Leu

65					70					75					80
Ala	Asp	Arg	Gln	Ala 85	Phe	His	Met	Glu	Gln 90	Leu	Lys	туг	Ala	Glu 95	Met
Arg	Ala	Arg	Gln 100	Glń	His	Phe	Gln	Gln 105	Met	His	Gln	Gln	Gln 110	Gln	Gln
Pro	Pro	Pro 115	Ala	Leu	Pro	Pro	Gly 120	Ser	Gln	Pro	Ile	Pro 125	Pro	Thr	Gly
Ala	Ala 130	Gly	Pro	Pro	Ala	Xaa 135	His	Gly	Leu	Ala	Val 140	Ala	Pro	Ala	Ser
Val 145	Val	Pro	Ala	Pro	Ala 150	Gly	Ser	Gly	Ala	Pro 155	Pro	Gly	Ser	Leu	Gly 160
Pro	Ser	Glu	Gln	Ile 165	Gly	Gln	Ala	Gly	Ser 170	Thr	Ala	Gly	Pro	Gln 175	Gln
Gln	Gln	Pro	Ala 180	Gly	Ala	Pro	Gln	Pro 185	Gly	Ala	Val	Pro	Pro 190	Gly	Val
Pro	Pro	Pro 195	Gly	Pro	His	Gly	Pro 200	Ser	Pro	Phe	Pro	Asn 205	Gln	Gln	Thr
Pro	Pro 210	Ser	Met	Met	Pro	Gly 215	Ala	Val	Pro	Gly	Ser 220	Gly	His	Pro	Gly
Val 225	Ala	Gly	Asn	Ala	Pro 230	Leu	Gly	Leu	Pro	Phe 235	Gly	Met	Pro	Pro	Pro 240
Pro	Pro	Pro	Pro	Ala 245	Pro	Ser	Ile	Ile	Pro 250	Phe	Gly	Ser	Leu	Ala 255	Asp
Ser	Ile	Ser	Ile 260	Asn	Leu	Pro	Ala	Pro 265	Pro	Asn	Leu	His	Gly 270	His	His
His	His	Leu 275	Pro	Phe	Ala	Pro	Gly 280	Thr	Leu	Pro	Pro	Pro 285	Asn	Leu	Pro
Val	Ser 290	Met	Ala	Asn	Pro	Leu 295	His	Pro	Asn	Leu	Pro 300	Ala	Thr	Thr	Thr
Met 305	Pro	Ser	Ser	Leu	Pro 310	Leu	Gly	Pro	Gly	Leu 315	Gly	Ser	Ala	Ala	Ala 320
3 ln	Ser	Pro	Ala	Ile 325	Val	Ala	Ala	Val	Gln 330	Gly	Asn	Leu	Leu	Pro 335	Ser
la	Ser	Pro	Leu	Pro	Asp	Pro	Gly	Thr	Pro	Leu	Pro	Pro	Asp	Pro	Thr

462

345

Ala Pro Ser Pro Arg His Gly His Pro Cys Xaa His Leu His Ser Glu 355 360 365

340

350

Glu Pro Ala Arg His Leu Ser Pro Ser Pro Pro Val Asp Ile Thr Val 375 Pro Gly Thr Ala Leu Pro Pro Pro Leu Gly Pro Ser Pro Ala Trp Arg 390 395 Val His His Tyr Val Arg Lys Ala Pro Ser Ala Pro Pro Lys Pro Ser 405 Pro Cys Leu Thr Glu Ala Cys Ile Phe Ile Ser Asp Tyr Ser Arg Thr 425 Ser Val <210> 507 <211> 303 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (165) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (280) <223> Xaa equals any of the naturally occurring L-amino acids Glu Tyr Val Phe Pro Ala Lys Lys Leu Gln Glu Tyr Arg Val Leu Ile Thr Thr Leu Ile Thr Ala Gly Ser Trp Ser Arg Pro Ser Phe Pro 25 Leu Ile Thr Ser His Thr Ser Ser Ser Met Arg Leu Ala Thr Ala Trp 35 Ser Leu Arg Ser Leu Val Ala Ile Ala Gly Leu Met Glu Val Lys Glu Thr Gly Asp Pro Gly Gly Gln Leu Val Leu Ala Gly Asp Pro Arg Gln WO 00/55173

65					70					75				•	80
Leu	Gly	Pro	Val	Leu 85	Arg	Ser	Pro	Leu	Thr 90	Gln	Lys	His	Gly	Leu 95	Gly
Tyr	Ser	Leu	Leu 100	Glu	Arg	Leu	Leu	Thr 105	Tyr	Asn	Ser	Leu	Туг 110	Lys	Lys
Gly	Pro	Asp 115	Gly	Туr	Asp	Pro	Gln 120	Phe	Ile	Thr	Lys	Leu 125	Leu	Arg	Asn
Tyr	Arg 130	Ser	His	Pro	Thr	Ile 135	Leu	Asp	Ile	Pro	Asn 140	Gln	Leu	Tyr	Tyr
Glu 145	Gly	Glu	Leu	Gln	Ala 150	Cys	Ala	Asp	Val	Val 155	Asp	Arg	Glu	Arg	Phe 160
Cys	Arg	Trp	Ala	Xaa 165	Leu	Pro	Arg	Gln	Gly 170	Phe	Pro	Ile	Ile	Phe 175	His
Gly	Val	Met	Gly 180	Lys	Asp	Glu	Arg	Glu 185	Gly	Asn	Ser	Pro	Ser 190	Phe	Phe
Asn	Pro	Glu 195	Glu	Ala	Ala	Thr	Val 200	Thr	Ser	Tyr	Leu	Lys 205	Leu	Leu	Leu
Ala	Pro 210	Ser	Ser	Lys	Lys	Gly 215	Lys	Ala	Arg	Leu	Ser 220	Pro	Arg	Ser	Val
Gly 225	Val	Ile	Ser	Pro	Туг 230	Arg	Lys	Gln	Val	Glu 235	Lys	Ile	Arg	Tyr	Cys 240
Ile	Thr	Lys	Leu	Asp 245	Arg	Glu	Leu	Arg	Gly 250	Leu	Asp	Asp	Ile	Lys 255	Asp
Leu	Lys	Val	Gly 260	Ser	Val	Glu	Glu	Phe 265	Gln	Gly	Gln	Glu	Arg 270	Ser	Val
Ile	Leu	11e 275	Ser	Thr	Val	Arg	Xaa 280	Ala	Arg	Ala	Leu	Cys 285	Ser	Trp	Ile
Trp	Thr 290	Leu	Ile	Trp	Val	Ser 295	Leu	Arg	Thr	Pro	Arg 300	Gly	Ser	Met	
<210)> 50	8													

<211> 250

<212> PRT

<213> Homo sapiens

<22															
	1> S														
	2> (_		_
<22	3> x	aa e	qual	s an	y of	the	nat	ural	ly o	ccur	ring	L-a	mino	aci	ds
	0> 5											_		_ •	
	Gln	Tyr	Leu			Thr	Glu	Glu		Leu	Glu	Lys	Glu		Xaa
1				5					10					15	
_						_			_	_	_	_	_		_
Lys	Val	Glu		Phe	Asp	Leu	Val		Lys	Pro	Ser	Tyr	Tyr	Val	Arç
			20					25					30		
-	a 1					.	-			•		m	~1 ~	~1 -	n 7 -
Leu	GIĀ		Leu	Ser	Thr	rys		His	ser	Arg	Ala		Gln	GIN	AL
		35					40					45			
т о	502	n	17-3	T	c1	7 l -	T	~1 ~	T	C 0 =	Cln	Cln	mh-	T10	car
neu	50	AIG	Vai	гЛа	GIU	55	гус	GIN	гуз	ser	60	GIII	Thr	TIE	261
	50					23					80				
Gln	Leu	Hic	Ser	ጥኮታ	Va 1	Hic	Len	Tla	Glu	Dhe	Δla	Ara	Lys	Aen	Va 1
65		11.1.0	001	1	70		Deu	110	Olu	75		9	-, -		80
0.5										, ,					•
ጥ _{ህ ፕ}	Ser	Ala	Asn	Gln	Lvs	Tle	Gln	Asn	Ala	Gln	Asp	Lvs	Leu	Tvr	Leu
-,-	001			85	ביים				90	 .		_,_		95	
Ser	Trp	Val	Glu	Trp	Lvs	Ara	Ser	Ile	Glv	Tvr	Asp	Asp	Thr	Asp	Glu
			100		-,, -	5		105	1	-1-			110		
Ser	His	Cys	Ala	Glu	His	Ile	Glu	Ser	Arq	Thr	Leu	Ala	Ile	Ala	Arc
		115					120		-			125			-
Asn	Leu	Thr	Gln	Gln	Leu	Gln	Thr	Thr	Cys	His	Thr	Leu	Leu	Ser	Asn
	130					135			-		140				
Ile	Gln	Gly	Val	Pro	Gln	Asn	Ile	Gln	Asp	Gln	Ala	Lys	His	Met	Gly
145					150					155					160
Val	Met	Ala	Gly	Asp	Ile	Tyr	Ser	Val	Phe	Arg	Asn	Ala	Ala	Ser	Phe
				165					170					175	
Lys	Glu	Val	Ser	Asp	Ser	Leu	Leu	Thr	Ser	Ser	Lys	Gly	Gln	Leu	Gln
			180					185		•			190		
Lys	Met	Lys	Glu	Ser	Leu	Asp	Asp	Val	Met	Asp	Tyr	Leu	Val	Asn	Asn
		195					200					205			
Thr	Pro	Leu	Asn	Trp	Leu	Val	Gly	Pro	Phe	Tyr	Pro	Gln	Leu	Thr	Glu
	210					215					220				
	Gln	Asn	Ala	Gln		Gln	Gly	Ala	Glu		Asp	Lys	Ser	Ser	
225					230					235					240

465

Glu Thr Gln Arg Ser Glu His Lys Thr His 245 250

<210> 509

<211> 98

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (97)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 509

His Glu Leu Trp Gly Cys Gly Pro Val Thr Pro Arg Arg Thr Ala Pro 1 5 10 15

Ser Gly Trp Ala Gln Ala Pro Leu Ser Asp Thr Ala Gln Val Tyr Met $20 \hspace{1cm} 25 \hspace{1cm} 30$

Glu Leu Gln Gly Leu Val Asp Pro Gln Ile Gln Leu Pro Leu Leu Ala 35 40 45

Ala Arg Ser Thr Ser Cys Arg Ser Ser Leu Ile Ala Ser Gln Pro Gly
50 55 60

Pro His Gln Lys Gly Arg Gln Gly Leu Arg Gly Asn Lys Ser Phe Leu 65 70 75 80

Pro Ser Ser Trp Asn Cys Gln Asn Trp Thr Arg Gln Pro Leu Thr Ser 85 90 95

Xaa Ser

<210> 510

<211> 392

<212> PRT

<213> Homo sapiens

<400> 510

Gly Ala Met Arg Gly Asp Arg Gly Arg Gly Arg Gly Arg Phe Gly
1 5 10 15

Ser Arg Gly Gly Pro Gly Gly Phe Arg Pro Phe Val Pro His Ile 20 25 30

Pro Phe Asp Phe Tyr Leu Cys Glu Met Ala Phe Pro Arg Val Lys Pro Ala Pro Asp Glu Thr Ser Phe Ser Glu Ala Leu Leu Lys Arg Asn Gln Asp Leu Ala Pro Asn Ser Ala Glu Gln Ala Ser Ile Leu Ser Leu Val Thr Lys Ile Asn Asn Val Ile Asp Asn Leu Ile Val Ala Pro Gly Thr Phe Glu Val Gln Ile Glu Glu Val Arg Gln Val Gly Ser Tyr Lys Lys Gly Thr Met Thr Thr Gly His Asn Val Ala Asp Leu Val Val Ile Leu 120 Lys Ile Leu Pro Thr Leu Glu Ala Val Ala Ala Leu Gly Asn Lys Val 135 Val Glu Ser Leu Arg Ala Gln Asp Pro Ser Glu Val Leu Thr Met Leu 150 155 Thr Asn Glu Thr Gly Phe Glu Ile Ser Ser Asp Ala Thr Val Lys 165 Ile Leu Ile Thr Thr Val Pro Pro Asn Leu Arg Lys Leu Asp Pro Glu 185 Leu His Leu Asp Ile Lys Val Leu Gln Ser Ala Leu Ala Ala Ile Arg 200 His Ala Arg Trp Phe Glu Glu Asn Ala Ser Gln Ser Thr Val Lys Val 210 Leu Ile Arg Leu Leu Lys Asp Leu Arg Ile Arg Phe Pro Gly Phe Glu Pro Leu Thr Pro Trp Ile Leu Asp Leu Leu Gly His Tyr Ala Val Met Asn Asn Pro Thr Arg Gln Pro Leu Ala Leu Asn Val Ala Tyr Arg Arg 260 Cys Leu Gln Ile Leu Ala Ala Gly Leu Phe Leu Pro Gly Ser Val Gly 280 Ile Thr Asp Pro Cys Glu Ser Gly Asn Phe Arg Val His Thr Val Met 300

Thr Leu Glu Gln Gln Asp Met Val Cys Tyr Thr Ala Gln Thr Leu Val 305 310 315 320

Arg Ile Leu Ser His Gly Gly Phe Arg Lys Ile Leu Gly Gln Glu Gly 325 330 335

Asp Ala Ser Tyr Leu Ala Ser Glu Ile Ser Thr Trp Asp Gly Val Ile 340 345 350

Val Thr Pro Ser Glu Lys Ala Tyr Glu Lys Pro Pro Glu Lys Lys Glu 355 360 365

Gly Glu Glu Glu Glu Glu Asn Thr Glu Glu Pro Pro Gln Gly Glu Glu 370 375 380

Glu Glu Ser Met Glu Thr Gln Glu 385 390

<210> 511

<211> 72

<212> PRT

<213> Homo sapiens

<400> 511

His Gly Gly Gly Lys Gly Arg Gln Val Gly Leu His Ser Val Gln Arg $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$

Pro Ala Arg Arg Glu Thr Ala Ala Ser Trp Gly Leu Cys Val Lys Ile 20 25 30

Pro Asp Leu Gly Val Ala Phe Val Tyr Lys Met Gln Glu Gly Lys Pro 35 40 45

Val Pro Asp Ser Ser Arg Gln His Ala Gln Leu Ser Gly Ser Pro Val

Ser Gln Gly Leu Ser Leu Pro Leu 65 70

<210> 512

<211> 181

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (14)

468

<223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (33) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (135) <223> Xaa equals any of the naturally occurring L-amino acids <400> 512 Gly Trp Cys Ser Cys Ala His Ser Ser Ala Trp Pro Gly Xaa Trp Gly 15 5 10 Ala Ser Gly Ile Pro Gln Gln Ala Pro Met Thr Val Cys Asp Gln Ala Xaa Pro Val Thr Phe Leu Leu His Leu Glu Gly Gly Asp Ile His 40 Thr Val Ser His Leu Ser Ser Pro Pro Pro Gly Val Ala His Arg Met 50 55 Gly Thr Gly Gly Ser Arg Asn Pro Asn Pro Ala Trp Leu Gly Gly Ala Leu Leu Val Arg Gly Arg Pro Ala Ser Leu Ala Pro Trp Gly His Ser 90 Trp Lys Arg Gly Leu Ala His Ala Pro Leu Arg Ala Gly Thr Cys Thr 100 105 Gly His Thr Arg His Ser Ala Cys Trp Asn Arg Trp Leu Cys Ser Cys 120 Ser Gly Pro Arg Ala Ala Xaa Leu Arg Pro Cys Thr Ser His Met His 130 135 140 Trp Thr Arg Ala Glu Thr Pro Val Cys Tyr Arg Ala Leu Val Leu Cys 145 150 Gly Pro Gly Ala Thr Ala Gln Ser Ser Gln Trp Arg Ser Thr Pro Leu 170

Asp Ser Ile Phe Phe

469

<210> 513 <211> 202 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (15) <223> Xaa equals any of the naturally occurring L-amino acids <400> 513 Leu Gly Asp Thr Ile Glu Gly Thr Pro Ala Gly Thr Val Pro Xaa Phe 5 10 Pro Gly Arg Pro Thr Arg Ala Ile Met Ala Gln Asp Gln Gly Glu Lys Glu Asn Pro Met Arg Glu Leu Arg Ile Arg Lys Leu Cys Leu Asn Ile 40 Cys Val Gly Glu Ser Gly Asp Arg Leu Thr Arg Ala Ala Lys Val Leu Glu Gln Leu Thr Gly Gln Thr Pro Val Phe Ser Lys Ala Arg Tyr Thr 70 75 Val Arg Ser Phe Gly Ile Arg Arg Asn Glu Lys Ile Ala Val His Cys 85 90 Thr Val Arg Gly Ala Lys Ala Glu Glu Ile Leu Glu Lys Gly Leu Lys 100 105 Val Arg Glu Tyr Glu Leu Arg Lys Asn Asn Phe Ser Asp Thr Gly Asn 120 Phe Gly Phe Gly Ile Gln Glu His Ile Asp Leu Gly Ile Lys Tyr Asp 130 135 Pro Ser Ile Gly Ile Tyr Gly Leu Asp Phe Tyr Val Val Leu Gly Arg 145 155 Pro Gly Phe Ser Ile Ala Asp Lys Lys Arg Arg Thr Gly Cys Ile Gly 170 Ala Lys His Arg Ile Ser Lys Glu Glu Ala Met Arg Trp Phe Gln Gln 180

Lys Tyr Asp Gly Ile Ile Leu Pro Gly Lys

200

470

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<210> 514
<211> 63
<212> PRT
<213> Homo sapiens
<220>
<221> SITE
<222> (1)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (2)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (5)
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<220>
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<222> (16)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (35)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 514
Xaa Xaa Lys Asn Xaa Ile Thr Pro Lys Glu Glu Ser Pro Pro His Xaa
                                    10
Ala Leu Leu Ser Lys Cys Leu Leu Thr Pro Ser Pro Lys Met Pro Pro
             20
Ile Leu Xaa Val Met Ala Ala Leu Gly Phe Glu Arg Arg Glu Phe Gly
Ser Thr Ser Val Glu Arg Val Gln Ser Arg Gln Leu Asp Cys Phe
                         55
<210> 515
<211> 218
<212> PRT
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<213> Homo sapiens

~22	0-														
<22	1> S	ITE													
<22	2> (151)													
				c an	v of	t he	nat	ural	1 v o	ccur	ring	L-a	mino	aci	ds
	J- 1.	uu 0	4	- u	, 01				-, -						
.00	۸.														
<22	0>														
<22	1> S	ITE													
<22	2> (209)													
<22	3> X	aa e	qual	s an	y of	the	nat	ural	ly o	ccur	ring	L-a	mino	acio	ds
			•		-				-		_				
<22	۸.														
	1> s														
<22	2> (211)													
<22	3> X	aa e	qual:	s an	y of	the	nat	ural	ly o	ccur	ring	L-a	mino	aci	ds
<40	0> 5	15													
			Ara	Glv	Cve	Gla	Ara	Pro	Aen	Δla	Val	T.eu	ጥህዮ	Ala	Arc
	LCu		9		C, S	O1	*** 9						-1-	15	5
1				5					10					15	
His	Tyr	Asn	Ile	Pro	Val	Ile	His	Ala	Phe	Arg	Arg	Ala	Val	Asp	Asp
			20					25					30		
Pro	Glv	T.e.u	Va 1	Dho	Aen	Gln	T.Au	Pro	T.ve	Met	Leu	ጥህዮ	Pro	Glu	TVY
FLO	GLY		Vai	FILE	ASII	GIII		FIO	nys	Met	Deu		110	014	- 1 -
		35					40					45			
His	Lys	Val	His	Gln	Met	Met	Arg	Glu	Gln	Ser	Ile	Leu	Ser	Pro	Ser
	50					55					60				
D==	m	C1	C1	m	A	C 0 M	T 0	D=0	A ~~	uio	Cln.	T 011	T 011	Crrc	Bho
	Tyr	GTU	GTĀ	туг		ser	Leu	PIQ	Arg		Gln	reu	rea	Cys	
65					70					75					80
Lys	Glu	Asp	Cys	Gln	Ala	Val	Phe	Gln	Asp	Leu	Glu	Gly	Val	Glu	Lys
•		•	_	85					90					95	
	-	a 1	••- 3		-	1	-	**- 1	.	~1 -	61. .	c	***	D	2
Val	Pne	GIY		ser	Leu	val	Leu		Leu	TIE	Gly	ser		PIO	ASP
			100					105					110		
Leu	Ser	Phe	Leu	Pro	Gly	Ala	Gly	Ala	Asp	Phe	Ala	Val	Asp	Pro	Asp
		115			-		120		•			125	_		_
a 1.		.				•		_			3	•		5 -	
GIn		Leu	ser	Ala	rys	Arg	Asn	Pro	Ile	Asp	Val	Asp	Pro	Pne	Thr
	130					135					140				
Tvr	Gln	Ser	Thr	Ara	Gln	Xaa	Glv	Leu	Tvr	Ala	Met	Glv	Pro	Leu	Ala
145				,	150		1		-,-	155		2			160
147					100					100					100
													_		
Gly	Asp	Asn	Phe	Val	Arg	Phe	Val	Gln	Gly	Gly	Ala	Leu	Ala	Val	Ala
				165					170					175	
Ser	Ser	Lev	Leu	Ara	Lvs	Glu	Gln	Asn	His	Leu	His	Ara	Gln	Pro	Trp
			180	9	-, -			185					190		
			100					100					130		

472

```
Ser Ser Leu Arg Gly Ile His Pro Leu Ile Asp Leu Lys Ser Gly Val
                            200
Xaa Pro Xaa Leu Val Lys Leu Thr Ala Gln
                        215
    210
<210> 516
<211> 41
<212> PRT
<213> Homo sapiens
<220>
<221> SITE
<222> (22)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 516
Asn Gly Arg Pro Asp Ser Thr Gly Pro Ala Ile Pro Gly Ile Leu Ser
                  5
Trp Gly Phe Glu Thr Xaa Leu Arg Asp Arg Glu Thr Asp Pro Arg Asn
          20
Val Leu Asn Cys Asn Gly Pro His Thr
<210> 517
<211> 250
<212> PRT
<213> Homo sapiens
<220>
<221> SITE
<222> (118)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (161)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (204)
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<223> Xaa equals any of the naturally occurring L-amino acids

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Gly 1	Phe	Asn	Arg	Ser 5	Phe	Cys	Gly	Arg	Asn 10	Ala	Thr	Val	Tyr	Gly 15	Lys
Gly	Val	туг	Phe 20	Ala	Arg	Arg	Ala	Ser 25	Leu	Ser	Val	Gln	Asp 30	Arg	Туг
Ser	Pro	Pro 35	Asn	Ala	Asp	Gly	His 40	Lys	Ala	Val	Phe	Val 45	Ala	Arg	Val
Leu	Thr 50	Gly	Asp	Tyr	Gly	Gln 55	Gly	Arg	Arg	Gly	Leu 60	Arg	Ala	Pro	Pro
Leu 65	Arg	Gly	Pro	Gly	His 70	Val	Leu	Leu	Arg	Tyr 75	Asp	Ser	Ala	Val	Asp 80
Cys	Ile	Cys	Gln	Pro 85	Ser	Ile	Phe	Val	Ile 90	Phe	His	Asp	Thr	Gln 95	Ala
Leu	Pro	Thr	His 100	Leu	Ile	Thr	Суз	Glu 105	Ala	Arg	Ala	Pro	Arg 110	Phe	Pro
Arg	Arg	Pro 115	Leu	Trp	Xaa	Pro	Gly 120	Pro	Leu	Pro	Arg	His 125	Leu	Thr	Glu
	130					135				Ala	140				
145					150					Pro 155					160
				165					170	Gly				175	
			180					185		Gly			190		
		195					200			Arg		205			
	210					215				Cys	220				
225					230					Lys 235	Lys	Lys	Lys	Lys	Lys 240
Lvs	LVS	LVS	T.VS	Lvs	Lvs	Lvs	Lvs	Lvs	Lvs						

474

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<210> 518
 <211> 100
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SITE
 <222> (3)
 <223> Xaa equals any of the naturally occurring L-amino acids
 <220>
 <221> SITE
 <222> (7)
 <223> Xaa equals any of the naturally occurring L-amino acids
 Asn Pro Xaa Lys Lys Leu Xaa Ile Leu Ile Lys Trp Pro Pro Pro Phe
                                     10
 Pro Pro Ser Phe Pro Pro Ser Pro Asn Ser Leu Ser Ser Ser Phe
                                 25
 Pro Pro Pro Leu Ser Leu Phe Ser Pro Ser Phe Thr Phe Leu Ile Ser
         35
                            40
 Val Lys Leu Glu Arg Phe Glu Ile Pro Ile Lys Val Arg Leu Ser Pro
Glu Pro Trp Thr Pro Glu Thr Gly Leu Val Thr Asp Ala Phe Lys Leu
                                        75
                     70
Lys Arg Lys Glu Leu Arg Asn His Tyr Leu Lys Asp Ile Glu Arg Met
                                     90
                 85
Tyr Gly Gly Lys
<210> 519
· <211> 60
<212> PRT
<213> Homo sapiens
<220>
<221> SITE
<222> (5)
<223> Xaa equals any of the naturally occurring L-amino acids
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<220> <221> SITE

475

<222> (17)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 519

His Glu Asp Gly Xaa Leu Met Gly Cys Arg His Arg Trp His Pro Arg

1 5 10 15

Xaa Val Pro Phe His Gln Thr Ser Pro Lys Thr Glu Leu Glu Ser Thr 20 25 30

Ile Phe Gly Ser Pro Arg Leu Ala Ser Gly Leu Phe Pro Glu Trp Gln 35 40 45

Ser Trp Gly Arg Met Glu Asn Leu Ala Ser Tyr Arg
50 55 60

<210> 520

<211> 120

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (25)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 520

Ser His Pro Tyr Ala Pro Ser Cys Gly Leu Arg Gly Pro Gly Ala Ala 1 5 10 15

Ser Arg Ala Arg Thr Arg Glu Arg Xaa Pro Gln Ala Glu Ala Glu Ala 20 25 30

Arg Ser Thr Pro Gly Pro Ala Gly Ser Arg Leu Gly Pro Glu Thr Phe $35 \hspace{1cm} 40 \hspace{1cm} 45$

Arg Gln Arg Phe Arg Gln Phe Arg Tyr Gln Asp Ala Ala Gly Pro Arg
50 55 60

Glu Ala Phe Arg Gln Leu Arg Glu Leu Ser Arg Gln Trp Leu Arg Pro 65 70 . 75 80

Asp Ile Arg Thr Lys Glu Gln Ile Val Glu Met Leu Val Gln Glu Gln 85 90 95

Leu Leu Ala Ile Leu Pro Glu Ala Ala Arg Ala Arg Arg Ile Arg Arg 100 105 110

Arg Thr Asp Val Arg Ile Thr Gly

476

115 120

<210> 521

<211> 96

<212> PRT

<213> Homo sapiens

<400> 521

Gly His Gln Thr Val Ser Pro Ser Thr Gly Ser Arg Val Thr Arg Met $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$

Phe Ser Leu Ile Ser Phe Ser His Val Phe Ile Lys Asp Ile Cys Lys
20 25 30

Leu Pro Lys Asp Glu Gly Thr Cys Arg Asp Phe Ile Leu Lys Trp Tyr 35 40 45

Tyr Asp Pro Asn Thr Lys Ser Cys Ala Arg Phe Trp Tyr Gly Gly Cys 50 55 60

Gly Gly Asn Glu Asn Lys Phe Gly Ser Gln Lys Glu Cys Glu Lys Val 65 70 75 80

Cys Ala Pro Val Leu Ala Lys Pro Gly Val Ile Ser Val Met Gly Thr 85 90 95

<210> 522

<211> 122

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (18)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 522

Asn Ser Gly Phe Arg Pro Lys Asn Pro Val Gly Arg Gly Glu Pro
1 5 10 15

Glu Xaa Cys Gly Gly Ala Gly Gly Leu Gly Cys Thr Leu Val Trp Gly 20 25 30

Gly Thr Gly Ala Ala Val Val Thr Gly Val Val Trp Leu Leu Pro

35 40

Asn Gly Gly Val Gly Val Gly Leu Leu Gly Pro Gln Ser Pro Val Gly 55 50

Gly Ser Asp Ser Ala Pro Tyr Ser Leu His Pro Ala Gly Arg Thr Trp 70

Gly Leu Arg Ser Glu Cys Ile Pro Pro Leu Ser Phe Asn Leu Ser Cys 85 90

Arg Thr His Ser Gly Pro Gly Ala Arg Leu Gly Glu Ala Gly Pro Asn 105

Tyr Gly Ser Arg Glu Leu Gln Val Pro Thr 115 120

<210> 523

<211> 94

<212> PRT

<213> Homo sapiens

<400> 523

Leu Ile Pro Gln Val Cys Cys Lys His Ser Met Glu Asp Thr Asp Asp 10

Ser Leu Val Leu Val Phe Leu Ser Ala Val Asn Val Gln Gln Phe Ala 25

Gln Glu Leu Gly Asp His Ile Cys Leu Ser Gly Gln Gly Ser Glu Val 35 40

His Trp Asn Leu Leu Arg Asn Leu Phe Val Lys Thr Ile Val Asn Asn 55

Tyr Cys Ile Phe Leu Gln Lys Tyr Ile Leu Glu Asn Cys Ile Leu Ser 70 75 65

Ile Lys Val Phe Leu Cys Lys Lys Lys Lys Lys Leu Val 90 85

<210> 524

<211> 93

<212> PRT

<213> Homo sapiens

<220>

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<221> SITE
<222> (78)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (86)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (93)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 524
Ser Ala Val Met Gly Arg Lys Lys Lys Gln Leu Lys Pro Trp Cys
                                10
Trp Tyr Cys Asn Arg Asp Phe Asp Asp Glu Lys Ile Leu Ile Gln His
Gln Lys Ala Lys His Phe Lys Cys His Ile Cys His Lys Lys Leu Tyr
                             40
Thr Gly Pro Gly Leu Ala Ile His Cys Met Gln Val His Lys Glu Thr
     50
                         55
Ile Asp Ala Val Pro Asn Ala Tyr Leu Gly Glu Gln Thr Xaa Ile Gly
                     70
                                         75
Asn Ile Trp Tyr Gly Xaa Tyr Ser Arg Lys Arg Tyr Xaa
                 85
<210> 525
<211> 324
<212> PRT
<213> Homo sapiens
<220>
<221'> SITE
<222> (323)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 525
Asp Leu Arg Leu Ser Arg Pro Glu Ala Val Glu Ala Glu Ala Met Met
```

Ala Ala Met Ala Thr Ala Arg Val Arg Met Gly Pro Arg Cys Ala Gln

25

30

Ala	Leu	Trp 35	Arg	Met	Pro	Trp	Leu 40	Pro	Val	Phe	Leu	Ser 45	Leu	Ala	Ala
Ala	Ala 50	Ala	Ala	Ala	Ala	Ala 55	Glu	Gln	Gln	Val	Pro 60	Leu	Val	Leu	Trp
Ser 65	Ser	Asp	Arg	Asp	Leu 70	Trp	Ala	Pro	Ala	Ala 75	Asp	Thr	His	Glu	Gly 80
His	Ile	Thr	Ser	Asp 85	Leu	Gln	Leu	Ser	Thr 90	Tyr	Leu	Asp	Pro	Ala 95	Leu
Glu	Leu	Gly	Pro 100	Arg	Asn	Val	Leu	Leu 105	Phe	Leu	Gln	Asp	Lys 110	Leu	Ser
Ile	Glu	Asp 115	Phe	Thr	Ala	Tyr	Gly 120	Gly	Val	Phe	Gly	Asn 125	Lys	Gln	Asp
Ser	Ala 130	Phe	Ser	Asn	Leu	Glu 135	Asn	Ala	Leu	Asp	Leu 140	Ala	Pro	Ser	Ser
Leu 145	Val	Leu	Pro	Ala	Val 150	Asp	Trp	Tyr	Ala	Val 155	Ser	Thr	Leu	Thr	Thr 160
Tyr	Leu	Gln	Glu	Lys 165	Leu	Gly	Ala	Ser	Pro 170	Leu	His	Val	Asp	Leu 175	Ala
			180		_			185					190	Leu	
Ile	Arg	Leu 195	Pro	Tyr	Thr	Ala	Ser 200	Ser	Gly	Leu	Met	Ala 205	Pro	Arg	Glu
	210		_			215			-		220			Thr	
225					230					235				Arg	240
				245					250					Gly 255	
			260	_				265					270	Pro	
		275					280					285		Asn	
Ser	Val 290	Ala	Tyr	Lys	Asp	Gln 295	Trp	Glu	Asp	Leu	Thr 300	Pro	Leu	Thr	Phe

480

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Gly Val Gln Glu Leu Asn Leu Thr Gly Ser Phe Trp Asn Asp Ser Phe 305 310 315 320
```

Ala Ser Xaa His

```
<210> 526
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<211> 66

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (2)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 526

Phe Xaa Val Ser Trp Thr Trp Lys Gln Val Ser Glu Phe Pro Gly Asp
1 5 10 15

Gln Arg Asp Glu Val Leu Gln Leu Pro Pro Ser Ser Cys Asn Leu Val 20 25 30

Ser Ser Gly Ala Gly Gly Glu Pro Glu Lys Leu Ala Ser Tyr Ile Thr $35 \hspace{1cm} 40 \hspace{1cm} 45$

Ser Leu Trp Leu Phe Phe Ile Cys Lys Thr Arg Ile Ile Leu Asn Cys 50 55 60

Lys Gly

65

<210> 527

<211> 62

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (40)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 527

Asn Thr Gln Leu Trp Phe Leu Cys Phe Pro Asn Cys Lys Ala Ala Asp 1 5 10 15

Asn Lys Thr Pro Gly Phe His Val Ser Ser Ala Met Ser Thr Leu Thr 20 25 30

Gln Ile Leu Lys Gln Asn Ser Xaa Asn Ala Val Leu Arg Ile Gln Leu 35 40 45

Leu Leu Lys Pro Ile Ser Ile Cys Ile Ile Thr Thr Asn Ile 50 55 60

<210> 528

<211> 122

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (80)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (104)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (105)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 528

Tyr Asn Lys Ile Glu Ile Met His Leu Val Met Trp Pro Thr Ser Leu 1 5 10 15

Leu Thr Thr Met Asp Cys Phe Gln Gln Gln Leu Ile Phe Trp Ser Val 20 25 30

Leu Arg Gly Ala Cys Met Ser Phe Val Thr Ser Gly Ser Thr Pro Ala 35 40 45

Val Lys Tyr Cys Phe His Leu Pro Leu Gln Lys Ala Ser Cys Leu Leu 50 55 60

Thr Ser Thr Ala Lys Ala Leu Phe Trp Thr Gly Tyr Leu Ile Lys Xaa 65 70 75 80

Ile Ser Val Arg Leu Cys Ser Val Ile Pro Ser Glu Pro Arg Phe Val
85 90 95

Ser Lys Ala Thr Val Leu Ser Xaa Xaa Pro Cys Val Trp Gly Gln Val

482

110 100 105 Ala Ile Pro Pro Met Ser Leu Val Ile Leu 115 120 <210> 529 <211> 182 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (25) <223> Xaa equals any of the naturally occurring L-amino acids Asp Arg Thr Arg Leu Ser Gln Ala Ser Thr Pro Thr Pro Val Cys Trp 10 Gly Leu Leu Gln Pro Pro Pro Trp Xaa Glu Ala Trp Tyr Arg Leu Thr His Arg Gly Leu Cys Gln Val Arg Phe Cys Arg Trp Ser Gln Ala Leu 35 40 Pro Glu Ala Arg Gly Gly Ala Trp Ala Gly Ser Pro Gly Glu Gly Gln Ala Gly Pro Arg Leu His Thr His Ile Gln Pro Ala Gly Leu Ser Ala 70 Val Leu Ser Pro Ser Leu Ser Ser Pro Ser Ser Ala Val Thr Leu Ser 90 Ser Pro Ser Leu Pro Ala Ser Pro Pro Ala Ala Pro Pro Val Lys Arg Met Thr Lys Asp Leu Ser Tyr Ala Gly Ser Lys Asn Gln Asn Phe Leu 120 Leu Ala Phe Ser Phe Val Ala Ser Pro Ala Pro Ala Leu Pro Val Ser 130 His Pro Gly Pro Arg Leu Glu Ala Ser Leu His Leu Ser Tyr Cys Phe

Lys Pro Lys Phe Thr Val Ser Val Gly Gln Asp Leu Leu Ser Pro

170

Pro Leu Leu His Pro Pro 180

<210> 530

<211> 183

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (6)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (79)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (80)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (81)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 530

Ala Leu Val Leu Gly Xaa Lys Ser Val Arg Met Ala Ser Ser Arg Met

1 5 10 15

Thr Arg Arg Asp Pro Leu Thr Asn Lys Val Ala Leu Val Thr Ala Ser 20 25 30

Thr Asp Gly Ile Gly Phe Ala Ser Pro Gly Val Trp Pro Arg Thr Gly
35 40 45

Pro Arg Gly Arg Gln Gln Pro Glu Ala Ala Glu Cys Gly Pro Gly Gly
50 55 60

Gly Thr Leu Gln Gly Glu Gly Leu Ser Val Thr Gly Thr Cys Xaa Xaa 65 70 75 80

Xaa Gly Lys Ala Glu Asp Arg Glu Arg Leu Val Ala Thr Ala Val Lys
85 90 95

Leu His Gly Gly Ile Asp Ile Leu Val Ser Asn Ala Ala Val Asn Pro 100 105 110

484

Phe Phe Gly Ser Ile Met Asp Val Thr Glu Glu Val Trp Asp Lys Leu 120 Trp Met Asp Lys Glu Lys Glu Glu Ser Met Lys Glu Thr Leu Arg Ile 135 Arg Arg Leu Gly Glu Pro Glu Asp Cys Ala Gly Ile Val Ser Phe Leu Cys Ser Glu Asp Ala Ser Tyr Ile Thr Gly Glu Thr Val Val Val Gly 170 Gly Gly Thr Pro Ser Arg Leu . 180 <210> 531 <211> 129 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (89) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (103) <223> Xaa equals any of the naturally occurring L-amino acids <400> 531 Asn Ser Ala Pro Leu Ser Pro Thr Gly Leu Gly Gln Gly His Thr Gly His Val Arg Phe Leu Ala Ala Val Gln Leu Pro Asp Gly Phe Asn Leu 20 Leu Cys Pro Thr Pro Pro Pro Pro Pro Asp Thr Gly Pro Glu Lys Leu Pro Ser Leu Glu His Arg Asp Ser Pro Trp His Arg Gly Pro Ala Pro Ala Arg Pro Lys Met Leu Val Ile Ser Gly Gly Asp Gly Tyr Glu Asp

Phe Arg Leu Ser Ser Gly Gly Kaa Ala Val Arg Leu Trp Val Glu

485

Thr Thr Ala Gln Thr Thr Xaa Ser Cys Gly Gly Cys Asp Pro Val Cys
100 105 110

Arg Gly Pro Gly Leu Ala Arg Pro Pro Ala Phe Ser Leu Leu Ala Ser 115 . 120 125

Pro

<210> 532

<211> 91

<212> PRT

<213> Homo sapiens

<400> 532

Gly Ala Ile Ala Ser Ser Gly Pro Thr Gly Gly Arg Val Arg Lys His 1 5 10 15

Gln Leu Leu Pro Gly Ala Val Arg Glu Trp Glu Gln Leu Trp Ala Pro 20 25 30

His Phe Arg Gln Val Leu Pro Lys Pro Ser Asp Ala Val Arg Pro Gly
35 40 45

Leu Pro Val Val Leu Phe Arg Leu Cys Phe Gln Asn Ala Phe Ile Ser 50 60

Ser Val Pro Phe Gly Pro His Lys Ser Pro Trp Gly Val Gly Gly 65 70 75 80

Leu Cys Arg His Pro His Phe Lys Ala Gly Ser

<210> 533

<211> 67

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (63)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 533

Asn Leu Cys Gln Val Gln Pro Thr Arg Leu Tyr Ser Ser Leu His Ser 1 5 10 15

Gly Leu His His Val Arg Gln Val Thr Gln Lys Ser Tyr Lys Val Ser 20 25 30 Val Ser 25 Ser Arg Ser Tyr Lys Val Ser 30 Yal Ser 50 Yal Ser 30 Yal Se

<220>

<221> SITE

<222> (141)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 534

Phe Asn Arg Arg Tyr Pro Lys Ile Gln Phe Ser Leu Ser Thr Gly Pro 1 5 10 15

Ser Gly Thr Met Leu Asp Gly Val Leu Glu Gly Lys Leu Asn Ala Ala 20 25 30

Phe Ile Asp Gly Pro Ile Asn His Thr Ala Ile Asp Gly Ile Pro Val

Tyr Arg Glu Glu Leu Met Ile Val Thr Pro Gln Gly Tyr Ala Pro Val
50 60

Thr Arg Ala Ser Gln Val Asn Gly Ser Asn Ile Tyr Ala Phe Arg Ala 65 70 75 80

Asn Cys Ser Tyr Arg Arg His Phe Glu Ser Trp Phe His Ala Asp Gly
85 90 95

Ala Ala Pro Gly Thr Ile His Glu Met Glu Ser Tyr His Gly Met Leu 100 105 110

Ala Cys Val Ile Ala Gly Ala Gly Ile Ala Leu Ile Pro Arg Ser Met
115 120 125

Leu Glu Ser Met Pro Gly His His Gln Val Glu Xaa Xaa Ala Val Ser 130 135 140

<210> 535

<211> 175

<212> PRT

<213> Homo sapiens

<400> 535

Arg Ala Pro Ala Arg Ile Ser Gly Gly Gly Ser Ala Met Val Gly Gly

1 10 15

Gly Gly Val Gly Gly Leu Leu Glu Asn Ala Asn Pro Leu Ile Tyr 20 25 30

Gln Arg Ser Gly Glu Arg Pro Val Thr Ala Gly Glu Glu Asp Glu Gln 35 40 45

Val Pro Asp Ser Ile Asp Ala Arg Glu Ile Phe Asp Leu Ile Arg Ser 50 60

Ile Asn Asp Pro Glu His Pro Leu Thr Leu Glu Glu Leu Asn Val Val 65 70 75 80

Glu Gln Val Arg Val Gln Val Ser Asp Pro Glu Ser Thr Val Ala Val 85 90 95

Ala Phe Thr Pro Thr Ile Pro His Cys Ser Met Ala Thr Leu Ile Gly
100 105 110

Leu Ser Ile Lys Val Lys Leu Leu Arg Ser Leu Pro Gln Arg Phe Lys
115 120 125

Met Asp Val His Ile Thr Pro Gly Thr His Ala Ser Glu His Ala Val 130 135 140

Asn Lys Gln Leu Ala Asp Lys Glu Arg Val Ala Ala Ala Leu Glu Asn 145 150 155 160

Thr His Leu Leu Glu Val Val Asn Gln Cys Leu Ser Ala Arg Ser 165 170 175

<210> 536

<211> 148

<212> PRT

<213> Homo sapiens

<400> 536

Gly Trp His Arg Thr His His Arg Gly Arg His Gln Ala Arg Glu Ala 1 5 10 15

Glu Glu Glu Ala Trp Ala Ala Ala Glu Pro Ile Lys Lys Val Arg Lys
20 25 30

Ser Leu Ala Leu Asp Ile Val Asp Glu Asp Val Lys Leu Met Met Ser 35 40 45

Thr Leu Pro Lys Ser Leu Ser Leu Pro Thr Thr Ala Pro Ser Asn Ser 50 55 60

Ser Ser Leu Thr Leu Ser Gly Ile Lys Glu Asp Asn Ser Leu Leu Asn 65 70 75 80

Gln Gly Phe Leu Gln Ala Lys Pro Glu Lys Ala Ala Val Ala Gln Lys 85 90 95

Pro Arg Ser His Phe Thr Thr Pro Ala Pro Met Ser Ser Ala Trp Lys 100 105 110

Thr Val Ala Cys Gly Gly Thr Arg Asp Gln Leu Phe Met Gln Glu Lys
115 120 125

Ala Arg Gln Leu Leu Gly Arg Leu Lys Pro Ser His Thr Ser Arg Thr 130 135 140

Leu Ile Leu Ser 145

<210> 537

<211> 70

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (41)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE <222> (42) <223> Xaa equals any of the naturally occurring L-amino acids Arg Pro Thr Arg Ser Ala Trp Trp Gly Arg Leu Leu Ser Arg Val Ser 10 Pro Gln Pro Arg Pro Ala Ser Pro Ser Val Ser Thr Arg Asn Gln Leu 25 Pro Glu Ala Arg Arg Gly Val Glu Xaa Xaa Glu Cys Glu Glu Thr Ala 40 Ala Ser Ala Glu Arg Ala Gly Pro Pro Arg Ala Leu Val Phe Gly Ala 55 Gln Ser Arg Ser Pro Gly <210> 538 <211> 206 <212> PRT <213> Homo sapiens <400> 538 Gly Glu Val Ser Ala Ser Gly Ile Ala Arg Arg Gly Gly Pro Met Ala Pro Leu Gly Gly Ala Pro Arg Leu Val Leu Leu Phe Ser Gly Lys Arg 20 Lys Ser Gly Lys Asp Phe Val Thr Glu Ala Leu Gln Ser Arg Leu Gly Ala Asp Val Cys Ala Val Leu Arg Leu Ser Gly Pro Leu Lys Glu Gln Tyr Ala Gln Glu His Gly Leu Asn Phe Gln Arg Leu Leu Asp Thr Ser 65 70 Thr Tyr Lys Glu Ala Phe Arg Lys Asp Met Ile Arg Trp Gly Glu Glu Lys Arg Gln Ala Asp Pro Gly Phe Phe Cys Arg Lys Ile Val Glu Gly 105 Ile Ser Gln Pro Ile Trp Leu Val Ser Asp Thr Arg Arg Val Ser Asp 120 115

PCT/US00/05881 WO 00/55173

490

Ile Gln Trp Phe Arg Glu Ala Tyr Gly Ala Val Thr Gln Thr Val Arg 135 Val Val Ala Leu Glu Gln Ser Arg Gln Gln Arg Gly Trp Val Phe Thr

150 155

Pro Gly Val Asp Asp Ala Glu Ser Glu Cys Gly Leu Asp Asn Phe Gly 165 170

Asp Phe Asp Trp Val Ile Glu Asn His Gly Val Glu Gln Arg Leu Glu 185

Glu Gln Leu Glu Asn Leu Ile Glu Phe Ile Arg Ser Arg Leu 200 195

<210> 539

<211> 350

<212> PRT

<213> Homo sapiens

<400> 539

Ser Thr Leu Ile Ala Phe Ile Val Ile Ser Thr Leu Phe Pro Leu Leu 5

Asp Met Thr Glu Ile Tyr Phe Ser Leu Leu Asp Glu Ile Val Asp Thr

Leu Gly Glu Gly Ala Phe Gly Lys Val Val Glu Cys Ile Asp His Lys 40

Ala Gly Gly Arg His Val Ala Val Lys Ile Val Lys Asn Val Asp Arg 50

Tyr Cys Glu Ala Ala Arg Ser Glu Ile Gln Val Leu Glu His Leu Asn 70

Thr Thr Asp Pro Asn Ser Thr Phe Arg Cys Val Gln Met Leu Glu Trp 90

Phe Glu His His Gly His Ile Cys Ile Val Phe Glu Leu Leu Gly Leu 100 105

Ser Thr Tyr Asp Phe Ile Lys Glu Asn Gly Phe Leu Pro Phe Arg Leu 120

Asp His Ile Arg Lys Met Ala Tyr Gln Ile Cys Lys Ser Val Asn Phe 130 , 135

Leu 145	His	Ser	Asn	Lys	Leu 150	Thr	His	Thr	Asp	Leu 155	Lys	Pro	Glu	Asn	11e
Leu	Phe	Val	Gln	Ser 165	Asp	Tyr	Thr	Glu	Ala 170	Tyr	Asn	Pro	Lys	Ile 175	Lys
Arg	Asp	Glu	Arg 180	Thr	Leu	Ile	Asn	Pro 185	Asp	Ile	Lys	Val	Val 190	Asp	Phe
Gly	Ser	Ala 195	Thr	туr	Asp	Asp	Glu 200	His	His	Ser	Thr	Leu 205	Val	Ser	Thr
Arg	His 210	Tyr	Arg	Ala	Pro	Glu 215	Val	Ile	Leu	Ala	Leu 220	Gly	Trp	Ser	Gln
Pro 225	Cys	Asp	Val	Trp	Ser 230	Ile	Gly	Cys	Ile	Leu 235	Ile	Glu	Tyr	Tyr	Leu 240
Gly	Phe	Thr	Val	Phe 245	Pro	Thr	His	Asp	Ser 250	Lys	Glu	His	Leu	Ala 255	Met
Met	Glu	Arg	Ile 260	Leu	Gly	Pro	Leu	Pro 265	Lys	His	Met	Ile	Gln 270	Lys	Thr
Arg	Lys	Arg 275	Lys	Tyr	Phe	His	His 280	Asp	Arg	Leu	Asp	Trp 285	Asp	Glu	His
Ser	Ser 290	Ala	Gly	Arg	Tyr	Val 295	Ser	Arg	Arg	Cys	Lys 300	Pro	Leu	Lys	Glu
Phe 305	Met	Leu	Ser	Gln	Asp 310	Val	Glu	His	Glu	Arg 315	Leu	Phe	Asp	Leu	Ile 320
Gln	Lys	Met	Leu	Glu 325	Tyr	Asp	Pro	Ala	Lys 330	Arg	Ile	Thr	Leu	Arg 335	Glu
Ala	Leu	Lys	His 340	Pro	Phe	Phe	Asp	Leu 345	Leu	Lys	Lys	Ser	Ile 350		

<210> 540

<211> 324

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (54)

<223> Xaa equals any of the naturally occurring L-amino acids

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<220>
<221> SITE
<222> (56)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (297)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
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<220>
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<222> (305)
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<220>
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<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (321)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 540
Gln Ala Thr Met Gly Asn Val Leu Ala Ala Ser Ser Pro Pro Ala Gly
                5
                                     10
Pro Pro Pro Pro Pro Ala Pro Ala Leu Val Gly Leu Pro Pro Pro
Pro Ser Pro Pro Gly Phe Thr Leu Pro Pro Leu Gly Gly Ser Leu Gly
                                                 45
         35
                             40
Ala Gly Thr Ser Thr Xaa Arg Xaa Ser Glu Arg Thr Pro Gly Ala Ala
                         55
Thr Ala Ser Ala Ser Gly Ala Ala Glu Asp Gly Ala Cys Gly Cys Leu
                    70
Pro Asn Pro Gly Thr Phe Glu Glu Cys His Arg Lys Cys Lys Glu Leu
                 85
                                    90
Phe Pro Ile Gln Met Glu Gly Val Lys Leu Thr Val Asn Lys Gly Leu
            100
                                105
                                                    110
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Ser	Asn	His 115	Phe	Gln	Val	Asn	His 120	Thr	Val	Ala	Leu	Ser 125	Thr	Ile	Gly
Glu	Ser 130	Asn	Tyr	His	Phe	Gly 135	Val	Thr	туг	Val	Gly 140	Thr	Lys	Gln	Leu
Ser 145	Pro	Thr	Glu	Ala	Phe 150	Pro	Val	Leu	Val	Gly 155	Asp	Met	Asp	Asn	Ser 160
Gly	Ser	Leu	Asn	Ala 165	Gln	Val	Ile	His	Gln 170	Leu	Gly	Pro	Gly	Leu 175	Arg
Ser	Lys	Met	Ala 180	Ile	Gln	Thr	Gln	Gln 185	Ser	Lys	Phe	Val	Asn 190	Trp	Glr
Val	Asp	Gly 195	Glu	Tyr	Arg	Gly	Ser 200	Asp	Phe	Thr	Ala	Ala 205	Val	Thr	Leu
Gly	Asn 210	Pro	Asp	Val	Leu	Val 215	Gly	Ser	Gly	Ile	Leu 220	Val	Ala	His	Туг
Leu 225	Gln	Ser	Ile	Thr	Pro 230	Cys	Leu	Ala	Leu	Gly 235	Gly	Glu	Leu	Val	Туг 240
His	Arg	Arg	Pro	Gly 245	Glu	Glu	Gly	Thr	Val 250	Met	Ser	Leu	Ala	Gly 255	Lys
Tyr	Thr	Leu	Asn 260	Asn	Trp	Leu	Ala	Thr 265	Val	Thr	Leu	Gly	Gln 270	Ala	Gly
Met	His	Ala 275	Thr	Tyr	Tyr	His	Lys 280	Ala	Ser	Asp	Gln	Leu 285	Gln	Val	Gly
Val	Glu 290	Phe	Glu	Ala	Ser	Thr 295	Arg	Xaa	Gln	Asp	Thr 300	Ser	Val	Ser	Xaa
Xaa 305	Val	Pro	Ala	Trp	Asn 310	Leu	Pro	Lys	Gly	Gln 315	Pro	Xaa	Leu	Ser	Lys 320
Xaa	Leu	Leu	Gly												

<210> 541

<211> 204

<212> PRT

<213> Homo sapiens

<400> 541

WO 00/55173

494

Arg Gly Pro Thr Phe Thr Pro Glu Ile Met Ala Ala Glu Asp Val Val 1 5 10 15

Ala Thr Gly Ala Asp Pro Ser Asp Leu Glu Ser Gly Gly Leu Leu His
20 25 30

Glu Ile Phe Thr Ser Pro Leu Asn Leu Leu Leu Gly Leu Cys Ile 35 40 45

Phe Leu Leu Tyr Lys Ile Val Arg Gly Asp Gln Pro Ala Ala Ser Gly 50 60

Asp Ser Asp Asp Asp Glu Pro Pro Pro Leu Pro Arg Leu Lys Arg Arg 65 70 75 80

Asp Phe Thr Pro Ala Glu Leu Arg Arg Phe Asp Gly Val Gln Asp Pro 85 90 95

Arg Ile Leu Met Ala Ile Asn Gly Lys Val Phe Asp Val Thr Lys Gly
100 105 110

Arg Lys Phe Tyr Gly Pro Glu Gly Pro Tyr Gly Val Phe Ala Gly Arg 115 120 125

Asp Ala Ser Arg Gly Leu Ala Thr Phe Cys Leu Asp Lys Glu Ala Leu 130 135 140

Lys Asp Glu Tyr Asp Asp Leu Ser Asp Leu Thr Ala Ala Gln Glu 145 150 150 165

Thr Leu Ser Asp Trp Glu Ser Gln Phe Thr Phe Lys Tyr His His Val

Gly Lys Leu Leu Lys Glu Gly Glu Glu Pro Thr Val Tyr Ser Asp Glu 180 185 190

Glu Glu Pro Lys Asp Glu Ser Ala Arg Lys Asn Asp 195 200

<210> 542

<211> 193

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (183)

<223> Xaa equals any of the naturally occurring L-amino acids

495

<4	0	0>	54	2
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Pro Ala Tyr Ser Leu Gly Leu Leu Lys Ser Val Leu Asp Gly Gly Gly 1 5 10 15

Ala Gly Ala His Gln Ala Arg Ser Asn Pro Ser Cys Met Tyr Pro Gln 20 25 30

Gly Thr Phe Val Ile Pro Leu Leu Val Thr Ala His Arg Asp Pro Thr . 35 40 45

Gln Phe Lys Asp Pro Asp Cys Phe Asn Pro Thr Asn Phe Leu Asp Lys
50 60

Gly Lys Phe Gln Gly Asn Asp Ala Phe Met Pro Phe Ala Ser Gly Ala 65 70 75 80

Gly Arg Gly Arg Gly Pro Ala Trp Thr Gly Ser Gly Val Pro Gly
- 85 90 95

Ala His Cys Ala Pro Val Tyr Pro Ala Lys Gln Met Cys Leu Gly Thr 100 105 110

Gly Leu Ala His Ser Gly Ile Phe Leu Phe Leu Thr Ala Thr Leu Gln 115 120 125

Arg Phe Cys Leu Leu Pro Val Val Arg Pro Gly Thr Ile Asn Leu Thr

Cys Ser Ala Leu Ala Trp Ala Val Ser Pro Gln Thr Ser Ser Ser 145 150 155 160

Gln Trp Pro Ala Glu Val Arg Leu His Tyr Gly Gly Leu Thr Gly Pro 165 170 175

Gln Thr Ser Île Pro Ser Xaa Val Asn Lys Gly Pro Lys Leu Gln Lys 180 185 190

Lys

<210> 543

<211> 352

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (5)

<223> Xaa equals any of the naturally occurring L-amino acids

<22 <22	0> 1> s:	ITE													
<22	2> (154)													
	•	•	qual	s an	y of	the	nat	ural	ly o	ccur	ring	L-a	mino	acio	is
<22	0>														
<22	1> S	ITE													
<22	2> (167)													
<22	3> X	aa e	qual:	s an	y of	the	nati	ural	ly o	ccur	ring	L-aı	mino	acio	is
	0> 5														
Ser 1	Thr	Val	Arg	Xaa 5	Pro	Gly	Arg	Pro	Thr 10	Arg	Pro	Met	Ala	Ala 15	Glu
Glu	Pro	Gln	Gln 20	Gln	Lys	Gln	Glu	Pro 25	Leu	Gly	Ser	Asp	Ser 30	Glu	Val
Leu	Thr	Val 35	Trp	Pro	Met	Met	Lys 40	Pro	Ser	Trp	Leu	Ser 45	Arg	Thr	Glu
Phe	Ser 50	Lys	Arg	Leu	Leu	Cys 55	Arg	Thr	Leu	Trp	Cys 60	Gln	Ser	Gly	Trp
Ser 65	Ser	Arg	Ser	Tyr	Thr 70	Arg	Ser	Met	Leu	Lys 75	Met	Thr	Thr	Ser	Ile 80
Asn	Arg	Arg	Ser	Arg 85	Thr	Ser	Thr	Lys	Ser 90	Thr	Arg	Thr	Ser	Ala 95	Arg
Pro	Gly	Leu	Thr 100	Ala	Thr	Val	Ser	Ile 105	Gly	Leu	Ser	Asp	Ser 110	Pro	Thr
Trp	Arg	His 115	Cys	Trp	Met	Thr	Ala 120	Arg	Ser	Суз	Ser	Gly 125	Glu	Lys	Gly
Gly	His 130	Trp	Ala	Pro	Arg	Gln 135	Val	Gly	Val	Tyr	Leu 140	Leu	Pro	Gly	Arg
Val 145	Gly	Cys	Val	Ser	Ser 150	Arg	Val	Ser	Xaa	Ser 155	Phe	Pro	Gly	Asp	Gly 160
Leu	Asp	Ser	Gly	Leu 165	Ala	Xaa	Arg	Gly	Ser 170	Ala	Val	Ser	Ala	Leu 175	Ala
Ser	Gly	Leu	Val 180	Glu	Glu	Pro	Met	Leu 185	Gly	Pro	Pro	Phe	His 190	Pro	Thr
Pro	Arg	Phe	Lys	Ala	Val	Ser	Ala 200	Lys	Ser	Lys	Glu	Asp 205	Leu	Val	Ser

Gln	Gly 210	Phe	Thr	Glu	Phe	Thr 215	Ile	Glu	Asp	Phe	His 220	Asn	Thr	Phe	Met
Asp 225	Leu	Ile	Glu	Gln	Val 230	Glu	Lys	Gln	Thr	Ser 235	Val	Ala	Asp	Leu	Le:
Ala	Ser	Phe	Asn	Asp 245	Gln	Ser	Thr	Ser	Asp 250	Tyr	Leu	Val	Val	Tyr 255	Leu
Arg	Leu	Leu	Thr 260	Ser	Gly	Tyr	Leu	Gln 265	Arg	Glu	Ser	Lys	Phe 270	Phe	Glu
His	Phe	Ile 275	Glu	Gly	Gly	Arg	Thr 280	Val	Lys	Glu	Phe	Cys 285	Gln	Gln	Glu
Val	Glu 290	Pro	Met	Cys	Lys	Glu 295	Ser	Asp	His	Ile	His 300	Ile	Ile	Ala	Leu
Ala 305	Gln	Ala	Leu	Ser	Val 310	Ser	Ile	Gln	Val	Glu 315		Met	Asp	Arg	Gly 320
Glu	Gly	Gly	Thr	Thr 325	Asn	Pro	His	Ile	Phe 330	Pro	Glu	Gly	Ser	Glu 335	Pro
Lys	Val	Tyr	Leu 340	Leu	Tyr	Arg	Pro	Gly 345	His	Tyr	Asp	Ile	Leu 350	Tyr	Lys

<210> 544

<211> 240

<212> PRT

<213> Homo sapiens

<400> 544

Ser Thr His Ala Ser Glu Met Ala Glu Arg Gly Tyr Ser Phe Ser Leu $1 \hspace{1.5cm} 5 \hspace{1.5cm} 10 \hspace{1.5cm} 15$

Thr Thr Phe Ser Pro Ser Gly Lys Leu Val Gln Ile Glu Tyr Ala Leu 20 25 30

Ala Ala Val Ala Gly Gly Ala Pro Ser Val Gly Ile Lys Ala Ala Asn

Gly Val Val Leu Ala Thr Glu Lys Lys Gln Lys Ser Ile Leu Tyr Asp 50 55 60

Glu Arg Ser Val His Lys Val Glu Pro Ile Thr Lys His Ile Gly Leu

498

65					70					75					80
Val	туг	Ser	Gly	Met 85	Gly	Pro	Asp	туг	Arg 90	Val	Leu	Val	His	Arg 95	Ala
Arg	Lys	Leu	Ala 100	Gln	Gln	Tyr	Tyr	Leu 105	Val	туг	Gln	Glu	Pro 110	Ile	Pro
Thr	Ala	Gln 115	Leu	Val	Gln	Arg	Val 120	Ala	Ser	Val	Met	Gln 125	Glu	Tyr	Thi
Gln	Ser 130	Gly	Gly	Val	Arg	Pro 135	Phe	Gly	Val	Ser	Leu 140	Leu	Ile	Cys	Gly
Trp 145	Asn	Glu	Gly	Arg	Pro 150	Tyr	Leu	Phe	Gln	Ser 155	Asp	Pro	Ser	Gly	Ala 160
Туг	Phe	Ala	Trp	Lys 165	Ala	Thr	Ala	Met	Gly 170	Lys	Asn	Tyr	Val	Asn 175	Gly
Lys	Thr	Phe	Leu 180	Glu	Lys	Arg	Tyr	Asn 185	Glu	Asp	Leu	Glu	Leu 190	Glu	Asp
Ala	Ile	His 195	Thr	Ala	Ile	Leu	Thr 200	Leu	Lys	Glu	Ser	Phe 205	Glu	Gly	Glr
Met	Thr 210	Glu	Asp	Asn	Ile	Glu 215	Val	Gly	Ile	Cys	Asn 220	Glu	Ala	Gly	Phe
Arg 225	Arg	Leu	Thr	Pro	Thr 230	Glu	Val	Lys	Asp	Tyr 235	Leu	Ala	Ala	Ile	Ala 240

<210> 545

<211> 181

<212> PRT

<213> Homo sapiens

<400> 545

Arg Cys Ile Leu Tyr Thr Gly Phe Met Leu Gly Ala Gln Arg Glu Val $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$

Asp Ser Arg Leu Leu Ala Leu Pro Gly Arg Lys Val Pro Thr Ser Trp

Trp Asp Asp Leu Phe Lys Gly Ala Lys Glu His Gly Ala Val Ala Val 35 40 45

Glu Arg Val Thr Lys Ser Pro Gly Glu Thr Ser Lys Pro Arg Pro Phe 55 Ala Gly Gly Gly Tyr Arg Leu Gly Ala Ala Pro Glu Glu Glu Ser Ala 70 75 Tyr Val Ala Gly Glu Lys Arg Gln His Ser Ser Gln Asp Val His Val 90 Val Leu Lys Leu Trp Lys Ser Gly Phe Ser Leu Asp Asn Gly Glu Leu 105 Arg Ser Tyr Gln Asp Pro Ser Asn Ala Gln Phe Leu Glu Ser Ile Arg 115 120 Arg Gly Glu Val Pro Ala Glu Leu Arg Arg Leu Ala His Gly Gly Gln 135 130 Val Asn Leu Asp Met Glu Asp His Arg Asp Glu Asp Phe Val Lys Pro 155 150 Lys Gly Ala Phe Lys Ala Phe Thr Gly Glu Gly Gln Lys Leu Gly Ser 170 165 Thr Ala Pro Arg Cys 180 <210> 546 <211> 197 <212> PRT <213> Homo sapiens Pro Arg Val Arg Arg Ala Arg Ala Ala Ala Gly Ser Ser His Ala Ala Met Ala Asp Ser Glu Leu Gln Leu Val Glu Gln Arg Ile Arg Ser 25 Phe Pro Asp Phe Pro Thr Pro Gly Val Val Phe Arg Asp Ile Ser Pro 35

Val Leu Lys Asp Pro Ala Ser Phe Arg Ala Ala Ile Gly Leu Leu Ala

Arg His Leu Lys Ala Thr His Gly Gly Arg Ile Asp Tyr Ile Ala Gly

, 75

55

Leu Asp Ser Arg Gly Phe Leu Phe Gly Pro Ser Leu Ala Gln Glu Leu $85 \hspace{1.5cm} 90 \hspace{1.5cm} 95$

Gly Leu Gly Cys Val Leu Ile Arg Lys Arg Gly Lys Leu Pro Gly Pro 100 105 110

Thr Leu Trp Ala Ser Tyr Ser Leu Glu Tyr Gly Lys Ala Glu Leu Glu 115 120 125

Ile Gin Lys Asp Ala Leu Glu Pro Gly Gln Arg Val Val Val Asp 130 135 140

Asp Leu Leu Ala Thr Gly Gly Thr Met Asn Ala Ala Cys Glu Leu Leu 145 150 155 160

Gly Arg Leu Gln Ala Glu Val Leu Glu Cys Val Ser Leu Val Glu Leu 165 170 175

Thr Ser Leu Lys Gly Arg Glu Lys Leu Ala Pro Val Pro Phe Ser 180 185 190

Leu Leu Gln Tyr Glu 195

<210> 547

<211> 93

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (84)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 547

Glu Thr Gly Lys Glu Ser Lys Ala Leu Phe Leu Pro Phe Pro Gly Ser 1 5 10 15

Val Tyr Ser Thr Ser Thr Gly Glu Ala Ser Gly Glu Gly Leu Ser Pro 20 25 30

Leu Pro His Leu His Glu Phe Trp Asn Ser Val Leu Leu Ala Ala Cys $35 \hspace{1cm} 40 \hspace{1cm} 45$

Phe Gln Leu Pro Pro Ile Ser Ile Ala Ala Gly Ser Ser Cys Leu Phe 50 60

Tyr Ser Val Ile Lys His Pro Ala Pro Thr Leu Ser Gln Arg Ser Ile
65 70 75 80

Leu Ile Leu Xaa Lys Lys Ile Tyr Glu Glu Lys Lys 85

<210> 548

<211> 49

<212> PRT

<213> Homo sapiens

<220> ·

<221> SITE

<222> (5)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 548

Gly Leu Gln Leu Xaa Ala His Ala Ala Gly Arg Val Pro Gly Cys Ala

Leu Gln Gly Leu Gly His Phe Leu Gln Glu Asn Lys Gln Leu Leu Arg

Asp Val Leu Ala Gln Glu Leu His Lys Pro Ala Phe Glu Gly Arg His 40

Ile

<210> 549

<211> 379

<212> PRT

<213> Homo sapiens

Val Ala Cys Cys Val Arg Ile Pro Gly Pro Pro Arg Arg Ser Gly Pro 5 15 10

Ala Met Ala Val Thr Ile Thr Leu Lys Thr Leu Gln Gln Gln Thr Phe 25

Lys Ile Arg Met Glu Pro Asp Glu Thr Val Lys Val Leu Lys Glu Lys 40

Ile Glu Ala Glu Lys Gly Arg Asp Ala Phe Pro Val Ala Gly Gln Lys 55

Leu Ile Tyr Ala Gly Lys Ile Leu Ser Asp Asp Val Pro Ile Arg Asp 70 75 65

Tyr	Arg	IIe	Asp	85	rys	Asn	Pne	Val	90	vai	Met	vai	Thi	95	1111
Lys	Ala	Gly	Gln 100	Gly	Thr	Ser	Ala	Pro 105	Pro	Glu	Ala	Ser	Pro 110	Thr	Ala
Ala	Pro	Glu 115	Ser	Ser	Thr	Ser	Phe 120	Pro	Pro	Ala	Pro	Thr 125	Ser	Gly	Met
Ser	His 130	Pro	Pro	Pro	Ala	Ala 135	'Arg	Glu	Asp	Lys	Ser 140	Pro	Ser	Glu	Glu
Ser 145	Ala	Pro	Thr	Thr	Ser 150	Pro	Glu	Ser	Val	Ser 155	Gly.	Ser	Val	Pro	Ser 160
Ser	Gly	Ser	Ser	Gly 165	Arg	Glu	Glu	Asp	Ala 170	Ala	Ser	Thr	Leu	Val 175	Thr
Gly	Ser	Glu	Tyr 180	Glu	Thr	Met	Leu	Thr 185	Glu	Ile	Met	Ser	Met 190	Gly	Tyr
		195					200				Ser	205			
	210					215					Pro 220				
225					2,30					235	Ser				240
				245					250		Arg			255	
			260		٠			265			Pro		270		
		275					280				Gln	285			
	290					295					Leu 300				
305					310					315	Glu				320
				325					330		Val			335	
Lys	Glu	Ala	11e 340	Glu	Arg	Leu	Lys	Ala 345	Leu	Gly	Phe	Pro	Glu 350	Ser	Leu

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Val Ile Gln Ala Tyr Phe Ala Cys Glu Lys Asn Glu Asn Leu Ala Ala
                             360
 Asn Phe Leu Leu Ser Gln Asn Phe Asp Asp Glu
                         375
 <210> 550
. <211> 275
 <212> PRT
<213> Homo sapiens
<220>
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 <222> (6)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
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<223> Xaa equals any of the naturally occurring L-amino acids
<220>
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<222> (260)
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<222> (261)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (267)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (272)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 550
Cys Ser Cys Lys Arg Xaa His Gln Gln Gln Val Leu Pro Pro Arg Gln
Pro Ser Ala Leu Val Pro Ser Val Thr Glu Tyr Arg Leu Asp Gly His
             20
                                                      30
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Thr	Ile	Ser 35	Asp	Leu	Ser	Arg	Ser 40	Ser	Arg	Gly	Glu	Leu 45	Ile	Pro	Ile
Ser	Pro 50	Ser	Thr	Glu	Val	Gly 55	Gly	Ser	Gly	Ile	Gly 60	Thr	Pro	Pro	Ser
Val 65	Leu	Lys	Arg	Gln	Arg 70	Lys	Arg	Arg	Val	Ala 75	Leu	Ser	Pro	Val	Thr 80
Glu	Asn	Ser	Thr	Ser 85	Leu	Ser	Phe	Leu	Asp 90	Ser	Cys	Asn	Ser	Leu 95	Thr
Pro	Lys	Ser	Thr 100	Pro	Val	Lys	Thr	Leu 105	Pro	Phe	Ser	Pro	Ser 110	Gln	Phe
Leu	Asn	Phe 115	Trp	Asn	Lys	Gln	Asp 120	Thr	Leu	Glu	Leu	Glu 125	Ser	Pro	Ser
Leu	Thr 130	Ser	Thr	Pro	Val	Cys 135	Ser	Gln	Lys	Val	Val 140	Val	Thr	Thr	Pro
Leu 145	His	Arg	Asp	Lys	Thr 150	Pro	Leu	His	Gln	Lys 155	His	Ala	Ala	Phe	Val
Thr	Pro	Asp	Gln	Lys 165	Tyr	Ser	Met	Asp	Asn 170	Thr	Pro	His	Thr	Pro 175	Thr
Pro	Phe	Lys	Asn 180	Ala	Leu	Glu	Lys	Туг 185	Gly	Pro	Leu	Lys	Pro 190	Leu	Pro
Gln	Thr	Pro 195	His	Leu	Glu	Glu	Asp 200	Leu	Lys	Glu	Val	Leu 205	Arg	Ser	Glu
Ala	Gly 210	Ile	Glu	Leu	Ile	Ile 215	Glu	Asp	Asp	Ile	Arg 220	Pro	Glu	Lys	Gln
Lys 225	Arg	Lys	Pro	Gly	Leu 230	Arg	Arg	Ser	Pro	Xaa 235	Lys	Lys	Val	Arg	Lys 240
Ser	Leu	Ala	Leu	Asp 245	Ile	Val	Asp	Glu	Asp 250	Val	Lys	Leu	Met	Met 255	Ser
Thr	Leu	Pro	Xaa 260	Xaa	Leu	Ser	Leu	Ala 265	Thr	Xaa	Ala	Pro	Cys 270	Lys	Xaa

<210> 551

Phe Gln Pro 275

PCT/US00/05881

50 55 60

Arg Phe Arg Cys Leu Glu Cys Gly Glu Arg Cys Ala Arg Ala Ala Asp 65 70 75 80

Leu Arg Ala His Arg Arg Thr His Ala Gly Gln Thr Leu Tyr Ile Cys $85 \hspace{1cm} 90 \hspace{1cm} 95$

Ser Glu Cys Gly Gln Ser Phe Arg His Ser Gly Arg Leu Asp Leu His 100 105 110

Leu Gly Ala His Arg Gln Arg Cys Arg Thr Cys Pro Cys Arg Thr Cys 115 120 125

Phe

<210> 552

<211> 405

<212> PRT

<213> Homo sapiens

<400> 552

Pro 1	Arg	Val	Arg	Arg 5	Arg	Ala	Arg	GIÀ	Arg 10	_	Val	Arg	Pro	15	GIŸ
Gly	Pro	Val	Arg 20	Arg	Gly	Ala	Ala	Val 25	Arg	Gly	Ala	Leu	Arg 30	Gly	Ala
Ser	Leu	Gly 35		Gly	Ala	Ala	Ala 40	Arg	Ala	Gly	Arg	Pro 45	Leu	Cys	Val
Arg	His 50	Ser	Glu	Pro	Val	Cys 55	Gly	Ser	Asp	Ala	Asn 60	Thr	Tyr	Ala	Asn
Leu 65	Cys	Gln	Leu	Arg	Ala 70	Ala	Ser	Arg	Arg	Ser 75	Glu	Arg	Leu	His	Arg 80
Pro	Pro	Val	Ile	Val 85	Leu	Gln	Arg	Gly	Ala 90	Cys	Gly	Gln	Gly	Gln 95	Glu
Asp	Pro	Asn	Ser 100	Leu	Arg	His	Lys	Туг 105	Asn	Phe	Ile	Ala	Asp 110	Val	Val
Glu	Lys	Ile 115	Ala	Pro	Ala	Val	Val 120	His	Ile	Glu	Leu	Phe 125	Arg	Lys	Leu
Pro	Phe 130	Ser	Lys	Arg	Glu	Val 135	Pro	Val	Ala	Ser	Gly 140	Ser	Gly	Phe	Ile
Val 145	Ser	Glu	Asp	Gly	Leu 150	Ile	Val	Thr	Asn	Ala 155	His	Val	Val	Thr	Asn 160
Lys	His	Arg	Val	Lys 165	Val	Glu	Leu	Lys	Asn 170	Gly	Ala	Thr	Tyr	Glu 175	Ala
		-	180		-		-	185	-		Ala		190	_	
-		195		-			200				Gly	205			
	210					215					Ser 220				
225					230	_				235	Thr				240
				245				-	250		Tyr			255	
Ala	Ile	Ile	Asn 260	Tyr	Gly	Asn	Ser	Gly 265	Gly	Pro	Leu	Val	Asn 270	Leu	Asp

507

Gly Glu Val Ile Gly Ile Asn Thr Leu Lys Val Thr Ala Gly Ile Ser 275 280 285

Phe Ala Ile Pro Ser Asp Lys Ile Lys Lys Phe Leu Thr Glu Ser His 290 295 300

Asp Arg Gln Ala Lys Gly Lys Ala Ile Thr Lys Lys Lys Tyr Ile Gly 305 310 315 320

Ile Arg Met Met Ser Leu Thr Ser Ser Lys Ala Lys Glu Leu Lys Asp 325 330 335

Arg His Arg Asp Phe Pro Asp Val Ile Ser Gly Ala Tyr Ile Ile Glu 340 345 350

Val Ile Pro Asp Thr Pro Ala Glu Ala Gly Gly Leu Lys Glu Asn Asp 355 360 365

Val Ile Ile Ser Ile Asn Gly Gln Ser Val Val Ser Ala Asn Asp Val 370 375 380

Ser Asp Val Ile Lys Arg Glu Ser Thr Leu Asn Met Val Val Arg Arg 385 390 395 400

Val Met Lys Ile Ser 405

<210> 553

<211> 107

<212> PRT

<213> Homo sapiens

<400> 553

Ala Gln Glu Asn Glu Glu Met Glu Gln Pro Met Gln Asn Gly Glu Glu 1 5 10 15

Asp Arg Pro Leu Gly Gly Gly Glu Gly His Gln Pro Ala Gly Asn Arg
20 25 30

Arg Gly Gln Ala Arg Arg Leu Ala Pro Asn Phe Arg Trp Ala Ile Pro $35 \hspace{1cm} 40 \hspace{1cm} 45$

Asn Arg Gln Ile Asn Asp Gly Met Gly Gly Asp Gly Asp Met Glu 50 60

Ile Phe Met Glu Glu Met Arg Glu Ile Arg Arg Lys Leu Arg Glu Leu 65 70 75 80

Gln Leu Arg Asn Cys Leu Arg Ile Leu Met Gly Glu Leu Ser Asn His

508

85 90 95

His Asp His His Asp Glu Phe Cys Leu Met Pro 100 105

<210> 554

<211> 229

<212> PRT

<213> Homo sapiens

<220>

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<222> (8)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (15)

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<223> Xaa equals any of the naturally occurring L-amino acids

<220>

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<222> (27)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (78)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 554

Gly Leu Ser Ala Glu Ser Thr Xaa Thr Ser Thr Met Pro Met Xaa Leu 1 5 10 15

Gly Tyr Trp Xaa Ile Arg Gly Leu Ala His Xaa Ile Arg Leu Leu 20 25 30

Glu Tyr Thr Asp Ser Ser Tyr Glu Glu Lys Lys Tyr Thr Met Gly Asp 35 40 45

Ala Pro Asp Tyr Asp Arg Ser Gln Trp Leu Asn Glu Lys Phe Lys Leu 50 60

Gly Leu Asp Phe Pro Asn Leu Pro Tyr Leu Ile Asp Gly Xaa His Lys

80 65 70 75 Ile Thr Gln Ser Asn Ala Ile Leu Arg Tyr Ile Ala Arg Lys His Asn 90 85 Leu Cys Gly Glu Ser Glu Lys Glu Gln Ile Arg Glu Asp Ile Leu Glu 105 100 Asn Gln Phe Met Asp Ser Arg Met Gln Leu Ala Lys Leu Cys Tyr Asp 120 Pro Asp Phe Glu Lys Leu Lys Pro Glu Tyr Leu Gln Ala Leu Pro Glu 130 135 Met Leu Lys Leu Tyr Ser Gln Phe Leu Gly Lys Gln Pro Trp Phe Leu 155 Gly Asp Lys Ile Thr Phe Val Asp Phe Ile Ala Tyr Asp Val Leu Glu 170 165 Arg Asn Gln Val Phe Glu Pro Ser Cys Leu Asp Ala Phe Pro Asn Leu 180 185 Lys Asp Phe Ile Ser Arg Phe Glu Gly Leu Glu Lys Ile Ser Ala Tyr 200 Met Lys Ser Ser Arg Phe Leu Pro Arg Pro Val Phe Thr Lys Met Ala 215 Val Trp Gly Asn Lys 225 <210> 555 <211> 106 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (59) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (60) <223> Xaa equals any of the naturally occurring L-amino acids

<220> <221> SITE

510

<222> (72) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (98) <223> Xaa equals any of the naturally occurring L-amino acids <400> 555 Asn Val Ile Ser Val Asp Pro Asn Asp Gln Lys Lys Thr Ala Cys Tyr Asp Ile Asp Val Glu Val Asp Asp Thr Leu Lys Thr Gln Met Asn Ser Phe Leu Leu Ser Thr Ala Ser Gln Gln Glu Ile Ala Thr Leu Asp Asn Lys Thr Met Thr Asp Val Val Gly Asn Gln Xaa Xaa Ser Ala Glu Leu Ser Ser Thr Ser Ser Pro Gly Xaa Gly Gly Cys Val Pro Ile Leu Leu Leu Gln Gly Ala Ala Glu Thr Thr Arg Ile Arg Ala Ser Pro Gly Asn 90 Pro Xaa Tyr Ile Gly Pro Leu Pro Gln Pro 100 <210> 556 <211> 86 <212> PRT <213> Homo sapiens Gly Arg Ala Thr Lys Gln Asn Thr Thr Lys Pro Asn His Arg Ile Ile 10 Phe Asn Pro Thr Phe Tyr Thr Met Pro Gln Phe Pro Ile Thr Leu His 25 Thr Ser Phe Cys Val Gln Leu Asn Cys Asn Cys Phe Leu Tyr Leu Glu 35 40 Arg Val Thr Ile Glu Leu Glu Thr Phe Tyr Ser Gly Arg Leu Gly Ser

55

Phe Trp Trp Asp Ser Val Gly Glu Arg Glu Glu Gly Glu Val Gly Gly

511

80 65 70 75 Leu Leu Pro Phe Arg Thr 85 <210> 557 <211> 565 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (57) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (71) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (75) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (82) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (118) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (120) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (552) <223> Xaa equals any of the naturally occurring L-amino acids <400> 557

Ala Ser Leu Thr Gly Thr Gln Ala Leu Pro Pro Leu Phe Ser Leu Gly

Tyr	His	Gln	Ser 20	Arg	Trp	Asn	Tyr	Arg 25	Asp	Glu	Ala	Asp	Val 30	Leu	Glu
Val	Asp	Gln 35	Gly	Phe	Asp	Asp	His 40	Asn	Leu	Pro	Cys	Asp 45	Val	Ile	Trp
Leu	Asp 50	Ile	Glu	His	Ala	Asp 55	Gly	Xaa	Arg	туг	Phe 60	Thr	Trp	Asp	Pro
Ser 65	Arg	Phe	Pro	Gln	Pro 70	Xaa	Thr	Met	Leu	Xaa 75	Arg	Leu	Ala	Ser	Lys 80
Arg	Xaa	Lys	Leu	Val 85	Ala	Ile	Val	Asp	Pro 90	His	Ile	Lys	Val	Asp 95	Ser
Gly	Tyr	Arg	Val 100	His	Glu	Glu	Leu	Arg 105	Asn	Leu	Gly	Leu	Tyr 110	Val	Lys
Thr	Arg	Asp 115	Gly	Ser	Xaa	Tyr	Xaa 120	Gly	Trp	Суѕ	Trp	Pro 125	Gly	Ser	Ala
	130					135					140			Ala	
Met 145	Phe	Ser	Tyr	Asp	Asn 150	Tyr	Glu	Gly	Ser	Ala 155	Pro	Asn	Leu	Phe	Val 160
				165					170					Val 175	
			180					185					190	Asp	
		195					200					205		Gly	
_	210			_	-	215					220			Arg	
225					230					235				Asp	240
				245			-		250					255	
			260					265					270	Gly	
Phe	Lys	Asn 275	Pro	Glu	Pro		Leu	Leu	Val	Arg	Trp	Tyr 285	Gln	Met	GLY

ATA	Tyr 290	GIn	Pro	Pne	Pne	Arg 295	Ala	HIS	Ala	HIS	300	Asp	Thr	GIŞ	AIG
Arg 305	Glu	Pro	Trp	Leu	Leu 310	Pro	Ser	Gln	His	Asn 315	Asp	Ile	Ile	Arg	Asp 320
Ala	Leu	Gly	Gln	Arg 325	Tyr	Ser	Leu	Leu	Pro 330	Phe	Trp	Tyr	Thr	Leu 335	Leu
Tyr	Gln	Ala	His 340	Arg	Glu	Gly	Ile	Pro 345	Val	Met	Arg	Pro	Leu 350	Trp	Val
Gln	Tyr	Pro 355	Gln	Asp	Val	Thr	Thr 360	Phe	Asn	Ile	Asp	Asp 365	Gln	Tyr	Leu
Leu	Gly 370	Asp	Ala	Leu	Leu	Val 375	His	Pro	Val	Ser	Asp 380	Ser	Gly	Ala	His
Gly 385	Val	Gln	Val	Tyr	Leu 390	Pro	Gly	Gln	Gly	Glu 395	Val	Trp	Tyr	Asp	Ile 400
		_	Gln	405					410					415	
			Ser 420					425					430		
-		435	Arg				440					445			
	450		Phe			455					460				
465			Asp		470					475					480
			Arg	485					490					495	
			Pro 500					505					510		
		515	Ile				520					525			
	530		Pro			535					540				
Ser 545	Val	Leu	Val	Leu	Arg 550	Lys	Xaa	Gly	Ile	Asn 555	Val	Ala	Ser	Asp	Trp 560

Ser Ile His Leu Arg 565

<210> 558

<211> 160

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (39)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 558

Arg Glu Ala Val Leu Pro Gln Ala Val Leu Arg His Pro Val Arg Thr
1 5 10 15

Gln Arg Arg Glu His Arg Gly Arg Gly Leu Leu His Leu Arg Glu Ala 20 25 30

Pro Gly Gly Gly Ala Ala Xaa His Arg Pro His Arg Gly Pro Arg Gly
35 40 45

Pro Ser Arg Gly Ala Glu Gly Glu Arg Pro Pro Glu Gly Pro Ser Arg
50 55 60

Ala Ser Ser Val Thr Thr Phe Thr Gly Glu Pro Asn Thr Cys Pro Arg 65 70 75 80

Cys Ser Lys Lys Val Tyr Phe Ala Glu Lys Val Thr Ser Leu Gly Lys 85 90 95

Asp Trp His Arg Pro Cys Leu Arg Cys Glu Arg Cys Gly Lys Thr Leu 100 105 110

Thr Pro Gly Gly His Ala Glu His Asp Gly Gln Pro Tyr Cys His Lys
115 120 125

Pro Cys Tyr Gly Ile Leu Phe Gly Pro Lys Gly Val Asn Thr Gly Ala 130 135 140

Val Gly Ser Tyr Ile Tyr Asp Arg Asp Pro Glu Gly Lys Val Gln Pro 145 150 155 160

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_	2> P 3> H		sapi	ens	•										
<40	0> 5	59													
Gly 1	Cys	Ile	Gly	туr 5	Leu	Val	Leu	Leu	Trp 10	Pro	Leu	Pro	Leu	Ile 15	His
Phe	Gly	Leu	Ala 20	Asn	Gln	Ser	Glu	Asp 25	Leu	Ser	Val	Phe	Туг 30	Pro	Gly
Thr	Leu	Leu 35	Glu	Thr	Gly	His	Asp 40	Ile	Leu	Phe	Phe	Trp 45	Val	Ala	Arg
Met	Val 50	Met	Leu	Gly	Leu	Lys 55	Leu	Thr	Gly	Arg	Leu 60	Pro	Phe	Arg	Glu
Val 65	Tyr	Leu	His	Ala	Ile 70	Val	Arg	Asp	Ala	His 75	Gly	Arg	Lys	·Met	Ser 80
Lys	Ser	Leu	Gly	Asn 85	Val	Ile	Asp	Pro	Leu 90	Asp	Val	Ile	Tyr	Gly 95	Ile
Ser	Leu	Gln	Gly 100	Leu	His	Asn	Gln	Leu 105	Leu	Asn	Ser	Asn	Leu 110	Asp	Pro
Ser	Glu	Val 115	Glu	Lys	Ala	Lys	Glu 120	Gly	Gln	Lys	Ala	Asp 125	Phe	Pro	Ala
Gly	Ile 130	Pro	Glu	Cys	Gly	Thr 135	Asp	Ala	Leu	Arg	Phe 140	Gly	Leu	Суз	Ala
Туг 145	Met	Ser	Gln	Gly	Arg 150	Asp	Ile	Asn	Leu	Asp 155	Val	Asn	Arg	Ile	Leu 160
Gly	Tyr	Arg	His	Phe 165	Cys	Asn	Lys	Leu	Trp 170	Asn	Ala	Thr	Lys	Phe 175	Ala
Leu	Arg	Gly	Leu 180	Gly	Lys	Gly	Phe	Val 185	Pro	Ser	Pro	Thr	Ser 190	Gln	Pro
Gly	Gly	His 195	Glu	Ser	Leu	Val	Asp 200	Arg	Trp	Ile	Arg	Ser 205	Arg	Leu	Thr
Glu	Ala 210	Val	Arg	Leu	Ser	Asn 215	Gln	Gly	Phe	Gln	Ala 220	Tyr	Asp	Phe	Pro
Ala 225	Val	Thr	Thr	Ala	Gln 230	Tyr	Ser	Phe	Trp	Leu 235	Tyr	Glu	Leu	Cys	Asp 240

Val	Tyr	Leu	Glu	Cys 245	Leu	Lys	Pro	Val	Leu 250	Asn	Gly	Val	Asp	Gln 255	Val
Ala	Ala	Glu	Cys 260	Ala	Arg	Gln	Thr	Leu 265	Tyr	Thr	Cys	Leu	Asp 270	Val	Gly
Leu	Arg	Leu 275	Leu	Ser	Pro	Phe	Met 280	Pro	Phe	Val	Thr	Glu 285	Glu	Leu	Phe
Gln	Arg 290	Leu	Pro	Arg	Arg	Met 295	Pro	Gln	Ala	Pro	Pro 300	Ser	Leu	Cys	Val
Thr 305	Pro	туг	Pro	Glu	Pro 310	Ser	Glu	Cys	Ser	Trp 315	Lys	Asp	Pro	Glu	Ala 320
Glu	Ala	Ala	Leu	Glu 325	Leu	Ala	Leu	Ser	Ile 330	Thr	Arg	Ala	Val	Arg 335	Ser
Leu	Arg	Ala	Asp 340	Tyr	Asn	Leu	Thr	Arg 345	Ile	Arg	Pro	Asp	Cys 350	Phe	Leu
Glu	Val	Ala 355	Asp	Glu	Ala	Thr	Gly 360	Ala	Leu	Ala	Ser	Ala 365	Val	Ser	Gly
Tyr	Val 370	Gln	Ala	Leu	Ala	Ser 375		Gly	Val	Val	Ala 380	Val	Leu	Ala	Leu
Gly 385	Ala	Pro	Ala	Pro	Gln 390	Gly	Cys	Ala	Val	Ala 395	Leu	Ala	Ser	Asp	Arg 400
Суѕ	Ser	Ile	His	Leu 405	Gln	Leu	Gln	Gly	Leu 410	Val	Asp	Pro	Ala	Arg 415	Glu
Leu	Gly	Lys	Leu 420	Gln	Ala	Lys	Arg	Val 425	Glu	Ala	Gln	Arg	Gln 430	Ala	Gln
Arg	Leu	Arg 435	Glu	Arg	Arg	Ala	Ala 440	Ser	Gly	Tyr	Pro	Val 445	Lys	Val	Pro
Leu	Glu 450	Val	Gln	Glu	Ala	Asp 455	Glu	Ala	Lys	Leu	Gln 460	Gln	Thr	Glu	Ala
Glu 465	Leu	Arg	Lys	Val	Asp 470	Glu	Ala	Ile	Ala	Leu 475	Phe	Gln	Lys	Met	Leu 480

PCT/US00/05881

<211> 96 <212> PRT

<213> Homo sapiens

<400> 560

Ala Cys Leu Glu Arg Cys Gly Ser Trp Arg Pro His Arg Pro Met Thr
1 5 10 15

Ser Gly Ala Arg Glu Asn Pro Ile Gln Val Pro Arg Ser Ser Leu Glu 20 25 30

Ala Thr Gly Ala Glu Arg Trp Ala Glu Asp Val Pro Tyr Pro Thr 35 40 45

Thr Arg Ala Val Ser Leu Pro Pro Ser Leu Gly Val Gly Ser Thr Gly 50 55 60

Met Ser Ser Ser Arg Phe Leu Gly Ser Leu Gly Lys His Gly Arg Leu 65 70 75 80

Asp Ser Ser Arg Arg Ala Arg Leu Trp Gly Arg Gly Gly Gly Gly 85 90 95

<210> 561

<211> 60

<212> PRT

<213> Homo sapiens

<400> 561

Ile Arg His Glu Ser Ser Ile Leu Ser Val Leu Phe Ile Arg Phe Leu 1 5 10 15

Lys Cys Ala Asp Pro Phe Lys Thr Pro Ala Tyr Leu Cys Asn Lys Glu 20 25 30

Lys Tyr Ser Lys Ile Leu Pro Ser Phe Ser His Thr Val Leu Lys Met 35 40 45

Leu Gln Asp Gln Ile Ile Ala His Lys Ile Arg Ser 50 55 60

<210> 562

<211> 241

<212> PRT

<213> Homo sapiens	<213>	Homo	sapiens
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<400> 562

Ser Ser Met Ala Lys Pro Cys Gly Val Arg Leu Ser Gly Glu Ala Arg

Lys Gln Val Glu Val Phe Arg Gln Asn Leu Phe Gln Glu Ala Glu Glu 20 25 30

Phe Leu Tyr Arg Phe Leu Pro Gln Lys Ile Ile Tyr Leu Asn Gln Leu 35 40 45

Leu Gln Glu Asp Ser Leu Asn Val Ala Asp Leu Thr Ser Leu Arg Ala 50 55 60

Pro Leu Asp Ile Pro Ile Pro Asp Pro Pro Pro Lys Asp Asp Glu Met
65 70 75 80

Glu Thr Asp Lys Gln Glu Lys Lys Glu Val Pro Lys Cys Gly Phe Leu 85 90 95

Pro Gly Asn Glu Lys Val Leu Ser Leu Leu Ala Leu Val Lys Pro Glu 100 105 110

Val Trp Thr Leu Lys Glu Lys Cys Ile Leu Val Ile Thr Trp Ile Gln 115 120 125

His Leu Ile Pro Lys Ile Glu Asp Gly Asn Asp Phe Gly Val Ala Ile 130 135 140

Gln Glu Lys Val Leu Glu Arg Val Asn Ala Val Lys Thr Lys Val Glu 145 150 155 160

Ala Phe Gln Thr Thr Ile Ser Lys Tyr Phe Ser Glu Arg Gly Asp Ala 165 170 175

Val Ala Lys Ala Ser Lys Glu Thr His Val Met Asp Tyr Arg Ala Leu 180 185 190

Val His Glu Arg Asp Glu Ala Ala Tyr Gly Glu Leu Arg Ala Met Val 195 200 205

Leu Asp Leu Arg Ala Phe Tyr Ala Glu Leu Tyr His Ile Ile Ser Ser 210 215 220

Asn Leu Glu Lys Ile Val Asn Pro Lys Gly Glu Glu Lys Pro Ser Met 225 230 235 240

Tyr

<210> 563 <211> 200 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (145) <223> Xaa equals any of the naturally occurring L-amino acids <400> 563 Leu Gly Ser Ile Gln Val Met Gln Ala Val Arg Asn Ala Gly Ser Arg 5 10 Phe Leu Arg Ser Trp Thr Trp Pro Gln Thr Ala Gly Arg Val Val Ala Arg Thr Pro Ala Gly Thr Ile Cys Thr Gly Ala Arg Gln Leu Gln Asp 40 Ala Ala Ala Lys Gln Lys Val Glu Gln Asn Ala Ala Pro Ser His Thr 50 55 Lys Phe Ser Ile Tyr Pro Pro Ile Pro Gly Glu Ser Ser Leu Arg Trp Ala Gly Lys Lys Phe Glu Glu Ile Pro Ile Ala His Ile Lys Ala 90 Ser His Asn Asn Thr Gln Ile Gln Val Val Ser Ala Ser Asn Glu Pro 100 105 Leu Ala Phe Ala Ser Cys Gly Thr Glu Gly Phe Arg Asn Ala Lys Lys Gly Thr Gly Ile Ala Ala Gln Thr Ala Gly Ile Ala Ala Ala Arg 135 Xaa Lys Gln Lys Gly Val Ile His Ile Arg Val Val Lys Gly Leu 150 145 Gly Pro Gly Arg Leu Ser Ala Met His Gly Leu Ile Met Gly Gly Leu 170 Glu Val Ile Ser Ile Thr Asp Asn Thr Pro Ile Pro His Asn Gly Cys 180 185

Arg Pro Arg Lys Ala Arg Lys Leu

520

<210> 564 <211> 115 <212> PRT <213> Homo sapiens <400> 564 Val Arg Leu Val Pro Gly Ala Asp Lys Tyr Asn Asp Asp Ile Arg Lys Gly Ile Val Leu Leu Glu Glu Leu Leu Pro Lys Gly Ser Lys Glu Glu Gln Arg Asp Tyr Val Phe Tyr Leu Ala Val Gly Asn Tyr Arg Leu Lys Glu Tyr Glu Lys Ala Leu Lys Tyr Val Arg Gly Leu Leu Gln Thr Glu 55 Pro Gln Asn Asn Gln Ala Lys Glu Leu Glu Arg Leu Ile Asp Lys Ala 70 Met Lys Lys Asp Gly Leu Val Gly Met Ala Ile Val Gly Gly Met Ala 85 90 Leu Gly Val Ala Gly Leu Ala Gly Leu Ile Gly Leu Ala Val Ser Lys 105 Ser Lys Ser 115 <210> 565 <211> 101 <212> PRT <213> Homo sapiens <400> 565 Pro Thr Arg Pro Asp Glu His Asp Glu Asn Asn Ala Glu Ala Ser Ala

Glu Leu Ser Asn Glu Gly Val Met Asn His Arg Ser Glu Glu Glu Arg

Val Thr Glu Thr Gln Lys Asn Glu Arg Val Lys Lys Gln Leu Gln Ala

Leu Ser Ser Glu Leu Ala Gln Ala Arg Asp Glu Thr Lys Lys Thr Gln

50 60 55 Asn Asp Val Leu His Ala Glu Asn Val Lys Ala Gly Arg Asp Lys Tyr 70 75 Lys Thr Leu Arg Gln Ile Arg Gln Gly Asn Thr Lys Gln Arg Ile Asp 90 Glu Phe Glu Ala Met 100 <210> 566 <211> 25 <212> PRT <213> Homo sapiens <400> 566 Thr Ala Asp Leu Val Ile Arg Pro Pro Arg Pro Leu Lys Val Leu Gly Phe Cys Val Phe Cys Ala Pro Pro Leu 20 <210> 567 <211> 274 <212> PRT <213> Homo sapiens <220> <221> SITE -<222> (182) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (216) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (222) <223> Xaa equals any of the naturally occurring L-amino acids

<223> Xaa equals any of the naturally occurring L-amino acids

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<222> (224)

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Val	Ala	Gly	Gly 20	Gln	Thr	Leu	Gly	Ala 25	Thr	Pro	Gly	Pro	Val 30	Met	Asr
Gly	Pro	Ala 35	Asp	Gly	Glu	Val	Asp 40	Tyr	Lys	Lys	Lys	Tyr 45	Arg	Asn	Let
Lys	Arg 50	Lys	Leu	Lys	Phe	Leu 55	Ile	Tyr	Glu	His	Glu 60	Cys	Phe	Gln	Glu
Glu 65	Leu	Arg	Lys	Ala	Gln 70	Arg	Lys	Leu	Leu	Lys 75	Val	Ser	Arg	Asp	Lys
Ser	Phe	Leu	Leu	Asp 85	Arg	Leu	Leu	Gln	Tyr 90	Glu	Asn	Val	Asp	Glu 95	Asp
Ser	Ser	Asp	Ser 100	Asp	Ala	Thr	Ala	Ser 105	Ser	Asp	Asn	Ser	Glu 110	Thr	Glu
Gly	Thr	Pro 115	Lys	Leu	Ser	Asp	Thr 120	Pro	Ala	Pro	Lys	Arg 125	Lys	Arg	Ser
Pro	Pro 130	Leu	Gly	Gly	Ala	Pro 135	Ser	Pro	Ser	Ser	Leu 140	Ser	Leu	Pro	Pro
Ser 145	Thr	Gly		Pro					-	Val 155	Pro	Ser	Pro	Tyr	
Ser	Ser	Leu	Ala	Ser 165	Ser	Arg	Tyr	Pro	Pro 170	Phe	Pro	Ser	Asp	Tyr 175	Leu
Ala	Leu	Gln	Leu 180	Pro	Xaa	Pro	Ser	Pro 185	Leu	Arg	Pro	Lys	Arg 190	Glu	Lys
Arg		Arg	Leu	Pro	Arg	-	Leu 200		Met	Ala	Val	Gly 205	Pro	Pro	Asp

Cys Pro Val Gly Gly Pro Leu Xaa Phe Pro Gly Arg Gly Xaa Gly Xaa 210 215 220 Gly Val Gly Xaa Thr Leu Xaa Pro Leu Pro Pro Pro Lys Met Pro Pro 230 235 Pro Thr Ile Leu Ser Thr Val Pro Arg Gln Met Phe Ser Asp Ala Gly 245 250 Ser Gly Asp Asp Ala Leu Asp Gly Asp Asp Leu Val Ile Asp Ile 260 265 Pro Glu <210> 568 <211> 133 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (47) <223> Xaa equals any of the naturally occurring L-amino acids

<400> 568

Ala Arg Gly Asp His Val Arg Ser Arg Glu Thr Gly Arg Gln Ser Ala

Ser Lys Gly Gln Ile Pro Leu Pro Arg Gly Pro Ala Val Pro Gly 20

Gly Pro Ser Ala Gln Thr Ala Ala Gln Arg Glu Leu Arg Gly Xaa Val

Gly Ala Gly Ala Pro Val Tyr Leu Ala Ala Val Leu Glu Tyr Leu Thr 55

Ala Glu Ile Leu Glu Leu Ala Gly Asn Ala Ala Arg Asp Asn Lys Lys

Thr Arg Ile Ile Pro Arg His Leu Gln Leu Ala Ile Arg Asn Asp Glu

Glu Leu Asn Lys Leu Leu Gly Lys Val Thr Ile Ala Gln Gly Gly Val

Leu Pro Asn Ile Gln Ala Val Leu Leu Pro Lys Lys Thr Glu Ser Gln 125 115 120

Lys Thr Lys Ser Lys 130 <210> 569 <211> 153 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (136) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (137) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (152) <223> Xaa equals any of the naturally occurring L-amino acids Met Cys Arg Gly Tyr Ala Trp Asn Pro Gly Ile Thr Leu Gln Asn Arg 10 Lys Thr Lys Glu Gly Pro Arg Ala Pro Pro Ser Arg Met Pro Glu Pro 25 Ala Gly Gly Leu Arg Gly Cys Glu Ala Val Gly Thr Leu Leu Met Lys 35 40 45 Glu Thr Val Phe Ala Leu His Pro Ser Leu Pro Leu Gly Ala Gly Ser 55 Ser Pro Ser Ala Thr Cys Ser Glu Gly Leu His Leu Arg Gly Glu Gly 70 75 Trp Gly Lys Ser Pro Pro Val Pro Phe Leu Trp Pro Cys Cys Pro His 85 90 Thr Gln Leu Arg Gly Pro Thr Leu Gly Lys Ala Gly Ser Ala Arg Ser 100 105 Leu Ser Pro Ile Ser Ala Leu Ser Ala Trp Ile Pro Ala Glu Ala Met 120 115

PCT/US00/05881 WO 00/55173

525

Lys Gly Asn Lys Glu Lys Arg Xaa Xaa Lys Lys Lys Lys Lys Lys 135

Lys Lys Lys Lys Lys Lys Xaa Pro 150

<210> 570

<211> 327

<212> PRT

<213> Homo sapiens

<400> 570

Pro Gly Ser Pro Arg Arg Cys Asp Ile Ile Ile Ser Gly Arg Lys 10

Glu Lys Cys Glu Ala Ala Lys Glu Ala Leu Glu Ala Leu Val Pro Val 25

Thr Ile Glu Val Glu Val Pro Phe Asp Leu His Arg Tyr Val Ile Gly

Gln Lys Gly Ser Gly Ile Arg Lys Met Met Asp Glu Phe Glu Val Asn

Ile His Val Pro Ala Pro Glu Leu Gln Ser Asp Ile Ile Ala Ile Thr 70 75

Gly Leu Ala Ala Asn Leu Asp Arg Ala Lys Ala Gly Leu Leu Glu Arg 85 90

Val Lys Glu Leu Gln Ala Glu Gln Glu Asp Arg Ala Leu Arg Ser Phe 105

Lys Leu Ser Val Thr Val Asp Pro Lys Tyr His Pro Lys Ile Ile Gly 115 120 125

Arg Lys Gly Ala Val Ile Thr Gln Ile Arg Leu Glu His Asp Val Asn 135

Ile Gln Phe Pro Asp Lys Asp Asp Gly Asn Gln Pro Gln Asp Gln Ile 150 155

Thr Ile Thr Gly Tyr Glu Lys Asn Thr Glu Ala Ala Arg Asp Ala Ile

Leu Arg Ile Val Gly Glu Leu Glu Gln Met Val Ser Glu Asp Val Pro 180 185

Leu Asp His Arg Val His Ala Arg Ile Ile Gly Ala Arg Gly Lys Ala

200 205 195 Ile Arg Lys Ile Met Asp Glu Phe Lys Val Asp Ile Arg Phe Pro Gln 215 Ser Gly Ala Pro Asp Pro Asn Cys Val Thr Val Thr Gly Leu Pro Glu 230 235 Asn Val Glu Glu Ala Ile Asp His Ile Leu Asn Leu Glu Glu Tyr 250 Leu Ala Asp Val Val Asp Ser Glu Ala Leu Gln Val Tyr Met Lys Pro 260 265 Pro Ala His Glu Glu Ala Lys Ala Pro Ser Arg Gly Phe Val Val Arg 280 Asp Ala Pro Trp Thr Ala Ser Ser Ser Glu Lys Ala Pro Asp Met Ser 295 Ser Ser Glu Glu Phe Pro Ser Phe Gly Ala Gln Val Ala Pro Lys Thr 305 315 310 Leu Pro Trp Gly Pro Lys Arg 325 <210> 571 <211> 166 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (9) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (12) <223> Xaa equals any of the naturally occurring L-amino acids Gly Asn Ser Arg Val Asp Pro Arg Xaa Arg Gly Xaa Ala His Thr Cys Ala Pro Cys Pro Ala Pro Gly Pro Leu Ala Gly Arg Ala Val Ser Gly

25

His Gly Ser Leu Pro Pro Asp Arg Ala Pro Ser Ala Leu Ser Ser

20

527

45 35 40 Pro Ala Asp Glu Gly Glu Arg Arg Pro Asp Leu Asp Glu Ile His 55 Arg Glu Leu Arg Pro Gln Gly Ser Ala Arg Pro Gln Pro Asp Pro Asn 70 Ala Glu Phe Asp Pro Asp Leu Pro Gly Gly Leu His Arg Cys Leu 90 Ala Cys Ala Arg Tyr Phe Ile Asp Ser Thr Asn Leu Lys Thr His Phe 100 105 Arg Ser Lys Asp His Lys Lys Arg Leu Lys Gln Leu Ser Val Glu Pro 120 Tyr Ser Gln Glu Glu Ala Glu Arg Ala Ala Gly Met Gly Ser Tyr Val 135 Pro Pro Arg Arg Leu Ala Val Pro Thr Glu Val Ser Thr Glu Val Pro 150 Glu Met Asp Thr Ser Thr 165 <210> 572 <211> 113 <212> PRT <213> Homo sapiens <400> 572 Gln Ser Ser Thr Phe His Pro Ala Pro Ala Phe Gly Ala Thr Val Ala Ala Phe His Arg Arg Ala Ala Leu Arg Ala Pro Glu Pro Ala Met Ser 25 Gly Pro Asn Gly Asp Leu Gly Met Pro Val Glu Ala Gly Ala Glu Gly Glu Glu Asp Gly Phe Gly Glu Ala Glu Tyr Ala Ala Ile Asn Ser Met Leu Asp Gln Ile Asn Ser Cys Leu Asp His Leu Glu Glu Lys Asn Asp His Leu His Ala Arg Leu Gln Glu Leu Leu Glu Ser Asn Arg Gln Thr 90 85

528

Arg Leu Glu Phe Gln Gln Gln Leu Gly Glu Ala Pro Ser Asp Ala Ser 100 105 110

Pro

<210> 573

<211> 99

<212> PRT

<213> Homo sapiens

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<222> (27)

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<220>

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<400> 573

Gly Ser Gly Ser Ser Arg Asp Leu His Lys Ala Leu Trp Glu Ala Gly
1 5 10 15

Trp Glu Thr Val Glu Gly Gly Cys Pro Leu Xaa Pro Arg Arg His Arg
20 25 30

Ile Trp Ala Leu Xaa Xaa Ala Phe Leu Pro Glu Tyr Ala Ala Ile Asn

Ser Met Leu Asp Gln Ile Asn Ser Cys Leu Asp His Leu Glu Glu Lys 50 55 60

Asn Asp His Leu His Ala Arg Leu Gln Glu Leu Leu Glu Ser Asn Arg 65 70 75 80

Gln Thr Arg Leu Glu Phe Gln Gln Gln Leu Gly Glu Ala Pro Ser Asp 85 90 95

Ala Ser Pro

PCT/US00/05881 WO 00/55173

529

<210> 574 <211> 197 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (97) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (124) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (129) <223> Xaa equals any of the naturally occurring L-amino acids <400> 574 Arg Trp Ala Arg Val Glu Ala Ala Val Met Glu Gly Ala Gly Ala Gly 10 Ser Gly Phe Arg Lys Glu Leu Val Ser Arg Leu Leu His Leu His Phe 25 Lys Asp Asp Lys Thr Lys Val Ser Gly Asp Ala Leu Gln Leu Met Val 35 40 Glu Leu Leu Lys Val Phe Val Val Glu Ala Ala Val Arg Gly Val Arg 55 Gln Ala Gln Ala Glu Asp Ala Leu Arg Val Asp Val Asp Gln Leu Glu 65 70 75 Lys Val Leu Arg Ser Cys Ser Gly Leu Leu Gly Ile Ser Ala Val Ala 85 Xaa Ala Thr Pro Arg Gly Ala Pro Gly Pro Gln Lys Gln Ala Leu Cys 105 Phe Gln Arg Pro Leu Ile Arg Gly Arg Glu Gly Xaa Glu Gly Phe Gly 115 120 Xaa Asp Ser Asn Lys Ile Ser Gly Ser Leu Gln Pro Val Gln Lys Gly 135 130 Gln Asp Cys Ser Ala Leu Arg Ala Leu Glu Cys Pro Val Gly Thr Leu

530

145 150 155 160

Val Trp Glu Gly Ala Ala Pro Gly Glu Ser Leu Pro Leu Leu Pro Gly 165 170 175

Thr Ile Val Cys Met Pro Pro Gly Val Leu Gln Ala Gly Ala Gly Lys 180 185 190

Gly Leu Ala Ser Arg 195

<210> 575

<211> 47

<212> PRT

<213> Homo sapiens

<400> 575

Leu Pro Met Val Asp Leu Met Glu Lys Leu Asn Ile Phe His Tyr Ala 1 5 10 15

Leu Gln Asn Thr Val Tyr Val Ser Ala Ser Leu Gly Asn Gly Arg Gly
20 25 30

Gln Lys Lys Val Thr Phe Asn Leu Cys Ile Phe Ala Lys Pro Tyr 35 40 45

<210> 576

<211> 115

<212> PRT

<213> Homo sapiens

<400> 576

Trp Ser Arg Thr Ser Gln Pro Leu Pro Ser Thr Val Gly Cys Pro Arg
1 5 10 15

Arg Arg Gly Phe Lys Asp Phe Gln Arg Arg Ile Leu Val Ala Thr Asn 20 25 30

Leu Phe Gly Arg Gly Met Asp Ile Glu Arg Val Asn Ile Ala Phe Asn 35 40 45

Tyr Asp Met Pro Glu Asp Ser Asp Thr Tyr Leu His Arg Val Ala Arg 50 60 .

Ala Gly Arg Phe Gly Thr Lys Gly Leu Ala Ile Thr Phe Val Ser Asp
65 70 75 80

Glu Asn Asp Ala Lys Ile Leu Asn Asp Val Gln Asp Arg Phe Glu Val 85 90

Asn Ile Ser Glu Leu Pro Asp Glu Ile Asp Ile Ser Ser Tyr Ile Glu 105

Gln Thr Arg 115

<210> 577

<211> 346

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

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<400> 577

Val Thr Ser Cys Val Ala Leu Leu Pro Ala Arg Arg Met Thr Tyr Thr 5 10

Thr Glu Thr Ala Leu Leu Asn Trp Ser Thr Cys Gln Met Val Leu Arg

Gly Ala Glu Thr Xaa Gly Cys Val Ile Val Ser Ala Ala Lys Ala Gln 40

Leu Leu Gln Cys Gln His His Pro Ala Trp Tyr Gly Asp Thr Leu Lys 55

Gln Lys Thr Ser Trp Thr Cys Leu Leu Asp Gly Met Gln Tyr Phe Ala 70 .

Thr Thr Glu Ser Ser Pro Thr Glu Gln Asp Gly Arg Gln Leu Trp Leu 85 90

Glu Val Lys Asn Ile Glu Glu His Arg Gln Arg Ser Leu Asp Ser Val

Gln Glu Leu Met Glu Ser Gly Gln Ala Val Gly Gly Met Val Thr Thr 120

Thr Thr Asp Trp Asn Gln Pro Ala Glu Ala Gln Gln Ala Gln Val

Gln Arg Ile Ile Ser Arg Cys Asn Cys Arg Met Tyr Tyr Ile Ser Tyr 155 150

532

Ser	His	Asp	Ile	Asp 165	Pro	Glu	Leu	Ala	Thr 170	Gln	Ile	Lys	Pro	Pro 175	Glu
Val	Leu	Glu	Asn 180	Gln	Glu	Lys	Glu	Asp 185	Leu	Leu	Lys	Lys	Gln 190	Glu	Gly
Ala	Val	Asp 195	Thr	Phe	Thr	Leu	Ile 200	His	His	Glu	Leu	Glu 205	Ile	Ser	Thr
Asn	Pro 210	Ala	Gln	туг	Ala	Met 215	Ile	Leu	Asp	Ile	Val 220	Asn	Asn	Leu	Leu
Leu 225	His	Val	Glu	Pro	Lys 230	Arg	Lys	Glu	His	Ser 235	Glu	Lys	Lys	Gln	Arg 240
Val	Arg	Phe	Gln	Leu 245	Glu	Ile	Ser	Ser	Asn 250	Pro	Glu	Glu	Gln	Arg 255	Ser
Ser	Ile	Leu	His 260	Leu	Gln	Glu	Ala	Val 265	Arg	Gln	His	Val	Ala 270	Gln	Ile
Arg	Gln	Leu 275	Glu	Lys	Gln	Met	Туг 280	Ser	Ile	Met	Lys	Ser 285	Leu	Gln	Asp
Asp	Ser 290	Lys	Asn	Glu	Asn	Leu 295	Leu	Asp	Leu	Asn	Gln 300	Lys	Leu	Gln	Leu
Gln 305	Leu	Asn	Gln	Glu	Lys 310	Ala	Asn	Leu	Gln	Leu 315	Glu	Ser	Glu	Glu	Leu 320
Asn	Ile	Leu	Ile	Arg 325	Cys	Phe	Lys	Asp	Phe 330	Gln	Leu	Gln	Arg	Ala 335	Asn
Lys	Met	Glu	Leu 340	Arg	Lys	His	Lys	Lys 345	Met						
<210	> 57	8													

<210> 578 <211> 91 <212> PRT <213> Homo sapiens

<400> 578

Arg His Glu Gly His Leu Gly Ser Gly Arg Asn Gly Gly Gly Ser Met

1 5 10 15

Asn Ala Pro Pro Ala Phe Glu Ser Phe Leu Leu Phe Glu Gly Glu Lys 20 25 30

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Ile Thr Ile Asn Lys Asp Thr Lys Val Pro Asn Ala Cys Leu Phe Thr
                                                  45
         35
                             40
Ile Asn Lys Glu Asp His Thr Leu Gly Asn Ile Ile Lys Ser Arg Ala
                         55
Cys Phe Pro Phe Ala Phe Cys Arg Asp Cys Gln Phe Pro Glu Ala Ser
                                         75
                     70
Pro Ala Thr Leu Pro Val Gln Pro Ala Glu Leu
                 85
<210> 579
<211> 331
<212> PRT
<213> Homo sapiens
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<222> (320)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
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-40	0> 5	70													
			Thr	Arg 5	Pro	Gly	Gly	Leu	Gly 10	Ser	Gly	Val	Leu	Ala 15	Leu
Ala	Xaa	Gly	Xaa 20	Pro	Ala	Arg	Leu	Ala 25	Gly	Thr	Val	His	Glu 30	Val	Gly
Asp	Ala	Pro 35	Arg	Arg	Ala	Pro	Asp 40	Gln	Ala	Ala	Glu	Ile 45	Gly	Ser	Arg
Gly	Ser 50	Thr	Lys	Ala	Gln	Gly 55	Pro	Gln	Gln	Gln	Pro 60	Gly	Ser	Glu	Gly
Pro 65	Ser	Tyr	Ala	Lys	Lys 70	Val	Ala	Leu	Trp	Leu 75	Ala	Gly	Leu	Leu	Gly 80
Ala	Gly	Gly	Thr	Val 85	Ser	Val	Val	Tyr	Ile 90	Phe	Gly	Asn	Asn	Pro 95	Val
Asp	Glu	Asn	Gly 100	Ala	Lys	Ile	Pro	Asp 105	Glu	Phe	Asp	Asn	Asp 110	Pro	Ile
Leu	Val	Gln 115	Gln	Leu	Arg	Arg	Thr 120	Tyr	Lys	туг	Phe	Lys 125	Asp [.]	Tyr	Arg
Gln	Met 130	Ile	Ile	Glu	Pro	Thr 135	Ser	Pro	Cys	Leu	Leu 140	Pro	Asp	Pro	Leu
Gln 145	Glu	Pro	Tyr	туг	Gln 150	Pro	Pro	туг	Thr	Leu 155	Val	Leu	Glu	Leu	Thr 160
Gly	Val	Leu	Leu	His 165	Pro	Glu	Trp	Ser	Leu 170	Ala	Thr	Gly	Trp	Arg 175	Phe
Lys	Lys	Arg	Pro 180	Gly	Ile	Glu	Thr	Leu 185	Phe	Gln	Gln	Leu	Ala 190	Pro	Leu
Tyr	Glu	Ile 195	Val	Ile	Phe	Thr	ser 200	Glu	Thr	Gly	Met	Thr 205	Ala	Phe	Pro
Leu	11e 210	Asp	Ser	Val	Asp	Pro 215	His	Gly	Phe	Ile	Ser 220	Tyr	Arg	Leu	Phe
Arg 225	Asp	Ala	Thr	Arg	Туг 230	Met	Asp	Gly	His	His 235	Val	Lys	Asp	Ile	Ser 240
Cys	Leu	Asn	Arg	Asp 245	Pro	Ala	Arg	Val	Val 250	Val	Val	Asp	Cys	Lys 255	Lys

535

Glu Ala Phe Arg Leu Gln Pro Tyr Asn Gly Val Ala Leu Arg Pro Trp 260 265 Asp Gly Asn Ser Asp Asp Arg Val Leu Leu Asp Leu Ser Ala Phe Leu 280 Lys Thr Ile Ala Leu Asn Gly Val Gly Gly Arg Xaa Glu Pro Cys Trp 295 Glu His Tyr Ala Leu Gly Xaa Asp Xaa Pro Arg Trp Ala Ala Phe Xaa 310 315 Asn Ser Gly Lys Xaa Gly Leu Glu Ala Gly Arg 325 <210> 580 <211> 374 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (235) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (285) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (307) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (319) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (324) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (341)

PCT/US00/05881 WO 00/55173

536

<223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (359) <223> Xaa equals any of the naturally occurring L-amino acids <400> 580 Pro Ser Thr Val Arg Asn Ser Arg Val Asp Pro Arg Val Arg Pro Arg Val Arg Ala Gly Val Ala Ala Leu Ala Thr Val Gly Val Ala Ser Gly Pro Gly Pro Gly Arg Pro Gly Pro Leu Gln Asp Glu Thr Leu Gly Val Ala Ser Val Pro Ser Gln Trp Arg Ala Val Gln Gly Ile Arg Gly Glu 55 Thr Lys Ser Cys Gln Thr Ala Ser Ile Ala Thr Ala Ser Ala Ser Ala 70 Gln Ala Arg Asn His Val Asp Ala Gln Val Gln Thr Glu Ala Pro Val 90 Pro Val Ser Val Gln Pro Pro Ser Gln Tyr Asp Ile Pro Arg Leu Ala 100 105 Ala Phe Leu Arg Arg Val Glu Ala Met Val Ile Arg Glu Leu Asn Lys 120 Asn Trp Gln Ser His Ala Phe Asp Gly Phe Glu Val Asn Trp Thr Glu 135 Gln Gln Gln Met Val Ser Cys Leu Tyr Thr Leu Gly Tyr Pro Pro Ala 145 155 150 Gln Ala Gln Gly Leu His Val Thr Ser Ile Ser Trp Asn Ser Thr Gly 165 170 Ser Val Val Ala Cys Ala Tyr Gly Arg Leu Asp His Gly Asp Trp Ser 185 Thr Leu Lys Ser Phe Val Cys Ala Trp Asn Leu Asp Arg Arg Asp Leu 195 200 Arg Pro Gln Gln Pro Ser Ala Val Val Glu Val Pro Ser Ala Val Leu 215

Cys Leu Ala Phe His Pro Thr Gln Pro Ser Xaa Val Ala Gly Gly Leu

235 240 225 230 Tyr Ser Gly Glu Val Leu Val Trp Asp Leu Ser Arg Leu Glu Asp Pro 250 245 Leu Leu Trp Arg Thr Gly Leu Thr Asp Asp Thr His Thr Asp Pro Val 265 Ser Gln Val Val Trp Leu Pro Glu Pro Gly His Ser Xaa Arg Phe Gln 280 Val Leu Ser Val Ala Thr Asp Gly Lys Val Leu Leu Trp Gln Gly Ile 295 Gly Val Xaa Gln Leu Gln Phe Thr Glu Gly Phe Ala Trp Phe Xaa Gln 305 310 315 Gln Leu Pro Xaa Ser Thr Lys Leu Lys Lys His Pro Arg Gly Arg Pro 325 330 Arg Trp Ala Pro Xaa Gln Ala Phe Phe Gln Phe Asp Leu Arg Phe Ser 350 340 345 Phe Trp Gln Glu Ala Val Xaa Val Gln Phe Ser Trp His Trp Arg Ala 365 360 Ala Leu Arg Gly Ala His 370 <210> 581 <211> 94 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (80) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (90) <223> Xaa equals any of the naturally occurring L-amino acids <400> 581 Cys Pro Asp Gln Asn Gly Trp Ala Ser Phe Gly Ala Pro Leu Ser Ala Gly Gly Gln Pro Cys Tyr Leu Leu Asp Ile Gly Cys Gly Ser Gly Leu

20 25 30

Ser Gly Asp Tyr Leu Ser Asp Glu Gly His Tyr Trp Val Gly Ile Asp 35 40 45

Ile Ser Pro Ala Met Leu Asp Ala Ala Leu Asp Arg Asp Thr Glu Gly 50 55 60

Asp Leu Leu Gly Asp Met Gly Gln Gly Ile Pro Phe Lys Pro Xaa 65 70 75 80

Ser Leu Met Asp Val Ser Ala Phe Cys Xaa Ser Val Ala Leu 85 90

<210> 582

<211> 163

<212> PRT

<213> Homo sapiens

<400> 582

Pro Thr Arg Pro Ala Ala Gly Gly Ala Glu Arg Ile Ala Gly Ser Ala 1 5 10 15

Met Ser Ser Glu Pro Pro Pro Pro Pro Gln Pro Pro Thr His Gln Ala
20 25 30

Ser Val Gly Leu Leu Asp Thr Pro Arg Ser Arg Glu Arg Ser Pro Ser 35 40 45

Pro Leu Arg Gly Asn Val Val Pro Ser Pro Leu Pro Thr Arg Arg Thr
50 55 60

Arg Thr Phe Ser Ala Thr Val Arg Ala Ser Gln Gly Pro Val Tyr Lys 65 70 75 80

Gly Val Cys Lys Cys Phe Cys Arg Ser Lys Gly His Gly Phe Ile Thr 85 90 95

Pro Ala Asp Gly Gly Pro Asp Ile Phe Leu His Ile Ser Asp Val Glu 100 105 110

Gly Glu Tyr Val Pro Val Glu Gly Asp Glu Val Thr Tyr Lys Met Cys 115 120 125

Ser Ile Pro Pro Lys Asn Glu Lys Leu Gln Ala Val Glu Val Val Ile 130 135 140

Thr His Leu Ala Pro Gly Thr Lys His Glu Thr Trp Ser Gly His Val 145 150 155 160

539

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Ile Ser Ser
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<210> 583
<211> 293
<212> PRT
<213> Homo sapiens
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<400> 583
Leu Leu Gly Pro Asn Leu Thr Met Gly Ser Gln Pro Gly Arg Ile Pro
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Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr

			20					25					30		
Ile	Asp	Val 35	Tyr	Met	Ile	Met	Val 40	Lys	Cys	Trp	Met	Ile 45	Asp	Ser	Glu
Cys	Arg 50	Pro	Xaa	Xaa	Arg	Glu 55	Leu	Val	Xaa	Glu	Phe 60	Ser	Arg	Met	Ala
Arg 65	Asp	Pro	Gln	Arg	Phe 70	Val	Val	Ile	Gln	Asn 75	Glu	Asp	Leu	Gly	Pro 80
Ala	Ser	Pro	Leu	Asp 85	Ser	Thr	Phe	Tyr	Arg 90	Ser	Leu	Leu	Glu	Asp 95	Asp
Asp	Met	Gly	Asp 100	Leu	Val	Asp	Ala	Glu 105	Glu	Tyr	Leu	Val	Pro 110	Gln	Gln
Gly	Phe	Phe 115	Cys	Pro	Asp	Pro	Ala 120	Pro	Gly	Ala	Gly	Gly 125	Met	Val	His
His	Arg 130	His	Arg	Ser	Ser	Ser 135	Thr	Arg	Ser	Gly	Gly 140	Gly	Asp	Leu	Thr
Leu 145	Gly	Leu	Glu	Pro	Xaa 150	Glu	Arg	Gly	Gly	Pro 155	Gln	Val	Ser	Thr	Gly 160
Thr	Leu	Arg	Arg	Ala 165	Gly	Ser	Asp	Val	Phe 170	Xaa	Gly	Asp	Leu	Gly 175	Met
Gly	Ala	Ala	Lys 180	Gly	Leu	Gln	Ser	Leu 185	Pro	Thr	His	Asp	Pro 190	Ser	Pro
Leu	Gln	Arg 195	Tyr	Ser	Glu	Asp	Pro 200	Thr	Val	Pro	Leu	Pro 205	Ser	Xaa	Thr
Asp	Gly 210	Tyr	Val	Ala	Pro	Leu 215	Thr	Cys	Ser	Pro	Gln 220	Pro	Glu	Tyr	Val
Asn 225	Gln	Pro	Asp	Val	Arg 230	Pro	Gln	Pro	Pro	Ser 235	Pro	Arg	Glu	Gly	Pro 240
Leu	Pro	Ala	Ala	Arg 245	Pro	Ala	Gly	Ala	Thr 250	Leu	Glu	Arg	Xaa	Lys 255	Thr
Leu	Ser	Pro	Gly 260	Lys	Asn	Gly	Val	Val 265		Glu	Phe	Leu	Pro 270	Leu	Gly
Val	Pro	Trp 275	Arg	Thr	Pro	Ser	Ile 280	Asp	Thr	Pro	Gly	Glu 285	Gly	Ala	Cys

Pro Ser Ala Pro Pro

PCT/US00/05881

290

<210> 584

<211> 132

<212> PRT

<213> Homo sapiens

<400> 584

Gly Gly Ala Gln Pro Gly Met Glu Gly Ala Ala Ala Thr Val His Leu
1 5 10 15

541

Ile Ser Gln Trp Ala Val Glu Pro Asn Ala Arg Val Gly Pro Leu Leu 20 25 30

Glu Val Glu Ala Ala Ala Ala Asp His His Glu Ala Ala Ala Gly Ala 35 40 45

Gly Ser Ala Val Glu Lys Ile Cys Ile Asp Lys Gly Leu Thr Asp Glu
50 60

Ser Glu Ile Leu Arg Phe Leu Gln His Gly Thr Leu Val Gly Leu Leu 65 70 75 80

Pro Val Pro His Pro Ile Leu Ile Arg Lys Tyr Gln Ala Asn Ser Gly 85 90 95

Thr Ala Met Trp Phe Arg Thr Tyr Met Trp Gly Val Ile Tyr Leu Arg 100 105 110

Asn Val Asp Pro Pro Val Trp Tyr Asp Thr Asp Val Lys Leu Phe Glu 115 120 125

Ile Gln Arg Val

<210> 585

<211> 218

<212> PRT

<213> Homo sapiens

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Arg Glu Arg Cys Arg Arg Glu Ala Leu Arg Gly Ser Arg Leu Cys Pro
                                     10
Ala Thr Pro Pro Ser Ala Leu Gly Ser Gln Asp Gly Ser Arg Thr Arg
             20
Asp Arg Leu Gly Ala Ala Gly Trp Pro Gly Leu Val Val Gly Leu Cys
                             40
Thr Pro Ala Ala Gly Xaa Gln Arg Asp Leu Leu His Arg Arg Gly Gly
Thr Ala Ser Phe Gly Lys Ser Phe Ala Gln Lys Ser Gly Tyr Phe Leu
 65
                     70
                                          75
Cys Leu Ser Ser Leu Gly Ser Leu Glu Asn Pro Xaa Glu Asn Val Val
                 85
                                     90
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PCT/US00/05881 WO 00/55173

543

Ala Asp Ile Gln Ile Val Val Asp Lys Ser Pro Leu Pro Leu Gly Phe 105 100 Ser Pro Val Cys Xaa Pro Met Asp Ser Lys Ala Ser Val Ser Lys Lys 120 Lys Arg Met Cys Val Lys Leu Leu Pro Leu Gly Xaa Xaa Asp Thr Ala 135 Val Phe Asp Val Arg Leu Ser Gly Lys Thr Lys Thr Val Pro Gly Tyr 155 150 Leu Arg Ile Gly Asp Met Gly Gly Phe Ala Ile Trp Cys Lys Lys Gly 165 170 Gln Gly Pro Glu Ala Ser Cys Pro Lys Pro Arg Xaa Pro Gln Pro Gly Thr Cys Lys Gly Phe Ser Xaa Xaa Ala Ala Ser Gln Pro Lys Leu Arg 200 Ala Gly Leu Leu Gly Ser Arg Thr Ser Val 215 210

<210> 586

<211> 233

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (41)

<223> Xaa equals any of the naturally occurring L-amino acids

Ala Arg Gly Glu Met Glu Gly Arg Gln Val Leu Glu Val Lys Met Gln

Val Glu Tyr Met Ser Phe Ser Ala His Ala Asp Ala Lys Gly Ile Met 25

Gln Leu Val Gly Gln Ala Glu Pro Xaa Ser Val Leu Leu Val His Gly

Glu Ala Lys Lys Met Glu Phe Leu Lys Gln Lys Ile Glu Gln Glu Leu

Arg Val Asn Cys Tyr Met Pro Ala Asn Gly Glu Thr Val Thr Leu Pro

544

. 75 70 80 65 Thr Ser Pro Ser Ile Pro Val Gly Ile Ser Leu Gly Leu Leu Lys Arg 90 Glu Met Ala Gln Gly Leu Leu Pro Glu Ala Lys Lys Pro Arg Leu Leu 105 His Gly Thr Leu Ile Met Lys Asp Ser Asn Phe Arg Leu Val Ser Ser Glu Gln Ala Leu Lys Glu Leu Gly Leu Ala Glu His Gln Leu Arg Phe Thr Cys Arg Val His Leu His Asp Thr Arg Lys Glu Gln Glu Thr Ala Leu Arg Val Tyr Ser His Leu Lys Ser Val Leu Lys Asp His Cys Val 165 170 175 Gln His Leu Pro Asp Gly Ser Val Thr Val Glu Ser Val Leu Leu Gln 185 Ala Ala Pro Ser Glu Asp Pro Gly Thr Lys Val Leu Leu Val Ser 200 Trp Thr Tyr Gln Asp Glu Glu Leu Gly Ser Phe Leu Thr Ser Leu Leu Lys Lys Gly Leu Pro Gln Ala Pro Ser 225 230 <210> 587 <211> 116 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (100) <223> Xaa equals any of the naturally occurring L-amino acids <400> 587 Gly Pro Leu Ser His His Ile Arg Ala Gln Leu Ser Lys Met Leu Leu 10 Ala Arg Lys Gln Ile Leu Cys Val Asn Val Lys Asn Phe Ala Val Ile

20

545

Tyr Leu Val Asp Ile Thr Glu Val Pro Asp Phe Asn Lys Met Tyr Glu

Leu Tyr Asp Pro Cys Thr Val Met Phe Phe Phe Arg Asn Lys His Ile 50 55 60

Met Ile Asp Leu Gly Thr Gly Asn Asn Lys Ile Asn Trp Ala Met
65 70 75 80

Glu Asp Lys Gln Glu Met Val Asp Ile Ile Glu Thr Val Tyr Arg Gly
85 90 95

Ala Arg Lys Xaa Arg Gly Leu Val Val Ser Pro Lys Asp Tyr Ser Thr 100 105 110

Lys Tyr Arg Tyr 115

<210> 588

<211> 133

<212> PRT

<213> Homo sapiens

<400> 588

Ala Arg Ala Ala Val Gly Arg Thr Ala Gly Val Arg Thr Trp Ala Pro

1 5 10 15

Leu Ala Met Ala Ala Lys Val Asp Leu Ser Thr Ser Thr Asp Trp Lys
20 25 30

Glu Ala Lys Ser Phe Leu Lys Gly Leu Ser Asp Lys Gln Arg Glu Glu 35 40 45

His Tyr Phe Cys Lys Asp Phe Val Arg Leu Lys Lys Ile Pro Thr Trp 50 55 60

Lys Glu Met Ala Lys Gly Val Ala Val Lys Val Glu Glu Pro Arg Tyr 65 70 75 80

Lys Lys Asp Lys Gln Leu Asn Glu Lys Ile Ser Leu Leu Arg Ser Asp 85 90 95

Ile Thr Lys Leu Glu Val Asp Ala Ile Val Asn Ala Ala Asn Ser Ser 100 105 110

Pro Pro Pro Arg Ser Leu Ile Lys Asp Leu Arg Cys Gly Lys Lys 115 120 125

Lys Lys Lys Lys

PCT/US00/05881 WO 00/55173

546

130

<210> 589

<211> 163

<212> PRT

<213> Homo sapiens

<400> 589

Arg His Arg Gly Gln Pro Leu Arg Gln Thr Arg Ala Ser Ser Pro

Gln Leu Ala Gly Arg Ser Ser Ser Val Leu Pro Ala Ala Ala Gln Pro 20

Cys Thr Pro Thr Met Asp Val Phe Lys Lys Gly Phe Ser Ile Ala Lys

Glu Gly Val Val Gly Ala Val Glu Lys Thr Lys Gln Gly Val Thr Glu 55

Ala Ala Glu Lys Thr Lys Glu Gly Val Met Tyr Val Gly Ala Lys Thr

Lys Glu Asn Val Val Gln Ser Val Thr Ser Val Ala Glu Lys Thr Lys 85

Glu Gln Ala Asn Ala Val Ser Glu Ala Val Val Ser Ser Val Asn Thr

Val Ala Thr Lys Thr Val Glu Glu Ala Glu Asn Ile Ala Val Thr Ser 120 115

Gly Val Val Arg Lys Glu Asp Leu Arg Pro Ser Ala Pro Gln Glu 135

Gly Glu Ala Ser Lys Glu Lys Glu Glu Val Ala Glu Glu Ala Gln Ser 145 150 155

Gly Gly Asp

<210> 590

<211> 59

<212> PRT

<213> Homo sapiens

<400> 590

547

Arg Ala Leu Leu Cys Leu Gly His His Pro Leu Leu Ala Gln Gly Val

1 10 15

Pro Ala Leu Ser Asp Met Arg Leu Pro Thr Leu Leu Pro Ser Ser Pro 20 25 30

Trp Pro Pro Leu Ala Cys Pro Pro Val Leu Leu His Gln Pro His Cys 35 40 45

Pro Pro Ser Ala Pro Pro Thr Leu Trp Ser Phe
50 55

<210> 591

<211> 116

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (31)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 591

Val His Ala Glu Ala Gly Arg Leu Cys His Gly Asp Cys Pro Arg Leu

1 5 10 15

Cys Arg Pro Arg Gln Arg Ser Ala Pro Val Gln Val Tyr Thr Xaa Arg
20 25 30

Gln Ala Ala Leu His Gly Arg Pro Gln Arg Asp Pro Cys Val Gly Gly
35 40 45

Pro Arg Pro Leu Arg Cys Ser Arg Asp Cys Gly Gly His Gln Arg
50 55 60

Leu Val Met Pro Gly Thr Trp Thr Gln Ala Trp Gln Arg Arg Gln Val 65 70 75 80

Val Asn Gly Leu Met Leu Gly Gln Ala Arg Ile His Val Asn Arg Leu
85 90 95

Glu Gln Ala Val Val Asn Leu Ala Pro Cys Glu Tyr Phe His Thr Cys 100 105 110

Cys Pro Phe Ala

115

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<210> 592
<211> 290
<212> PRT
<213> Homo sapiens
<220>
<221> SITE
<222> (30)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (239)
<223> Xaa equals any of the naturally occurring L-amino acids
Arg Arg Ser Leu Asn Thr His Gly Ser Gly Val Ser Val Cys Leu Gln
Ser Leu Thr Leu Leu Ala Thr Leu Cys Pro Gly Asp Gln Xaa Ser Leu
                                 25
Gly Leu Leu Thr Pro Cys Tyr Ser Gly Ser Glu Pro Ser Gly Thr Phe
Gly Pro Val Asn Pro Ser Leu Asn Asn Thr Tyr Glu Phe Met Ser Thr
Phe Phe Leu Glu Val Ser Ser Val Phe Pro Asp Phe Tyr Leu His Leu
 65
                     70
                                         75
Gly Gly Asp Glu Val Asp Phe Thr Cys Trp Lys Ser Asn Pro Glu Ile
                 85
Gln Asp Phe Met Arg Lys Lys Gly Phe Gly Glu Asp Phe Lys Gln Leu
                                105
Glu Ser Phe Tyr Ile Gln Thr Leu Leu Asp Ile Val Ser Ser Tyr Gly
        115
                            120
Lys Gly Tyr Val Val Trp Gln Glu Val Phe Asp Asn Lys Val Lys Ile
                        135
Gln Pro Asp Thr Ile Ile Gln Val Trp Arg Glu Asp Ile Pro Val Asn
                    150
                                        155
Tyr Met Lys Glu Leu Glu Leu Val Thr Lys Ala Gly Phe Arg Ala Leu
                165
Leu Ser Ala Pro Trp Tyr Leu Asn Arg Ile Ser Tyr Gly Pro Asp Trp
            180
                                185
```

549

Lys Asp Phe Tyr Val Val Glu Pro Leu Ala Phe Glu Gly Thr Pro Glu 200 Gln Lys Ala Leu Val Ile Gly Gly Glu Ala Cys Met Trp Gly Glu Tyr 210 215 Val Asp Asn Thr Asn Leu Val Pro Arg Leu Trp Pro Arg Ala Xaa Ala 230 235 Val Ala Glu Arg Leu Trp Ser Asn Lys Leu Thr Ser Asp Leu Thr Phe 245 250 Ala Tyr Glu Arg Leu Ser His Phe Arg Cys Glu Leu Leu Arg Arg Gly 260 265 Val Gln Ala Gln Pro Leu Asn Val Gly Phe Cys Glu Gln Glu Phe Glu 275 280 285 Gln Thr 290 <210> 593 <211> 665 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (8) <223> Xaa equals any of the naturally occurring L-amino acids Asp Ala Asp Gly Arg Met Asp Xaa Leu Val Ser Glu Cys Ser Ala Arg Leu Leu Gln Gln Glu Glu Glu Ile Lys Ser Leu Thr Ala Glu Ile Asp Arg Leu Lys Asn Cys Gly Cys Leu Gly Ala Ser Pro Asn Leu Glu Gln

Leu Gln Glu Glu Asn Leu Lys Leu Lys Tyr Arg Leu Asn Ile Leu Arg

Lys Ser Leu Gln Ala Glu Arg Asn Lys Pro Thr Lys Asn Met Ile Asn

Ile Ile Ser Arg Leu Gln Glu Val Phe Gly His Ala Ile Lys Ala Ala

55

				85					90					95	
туг	Pro	Asp	Leu 100	Glu	Asn	Pro	Pro	Leu 105	Leu	Val	Thr	Pro	Ser 110	Gln	Gln
Ala	Lys	Phe 115	Gly	Asp	Tyr	Gln	Cys 120	Asn	Ser	Ala	Met	Gly 125	Ile	Ser	Gln
Met	Leu 130	Lys	Thr	Lys	Glu	Gln 135	Lys	Val	Asn	Pro	Arg 140	Glu	Ile	Ala	Glu
Asn 145	Ile	Thr	Lys	His	Leu 150	Pro	Asp	Asn	Glu	Сув 155	Ile	Glu	Lys	Val	Glu 160
Ile	Aļa	Gly	Pro	Gly 165	Phe	Ile	Asn	Val	Нis 170	Leu	Arg	Lys	Asp	Phe 175	Val
Ser	Glu	Gln	Leu 180	Thr	Ser	Leu	Leu	Val 185	Asn	Gly	Val	Gln	Leu 190	Pro	Ala
Leu	Gly	Glu 195	Asn	Lys	Lys	Val	Ile 200	Val	Asp	Phe	Ser	Ser 205	Pro	Asn	Ile
Ala	Lys 210	Glu	Met	His	Val	Gly 215	His	Leu	Arg	Ser	Thr 220	Ile	Ile	Gly	Glu
Ser 225	Ile	Ser	Arg	Leu	Phe 230	Glu	Phe	Ala	Gly	Tyr 235	Asp	Val	Leu	Arg	Leu 240
Asn	His	Val	Gly	Asp 245	Trp	Gly	Thr	Gln	Phe 250	Gly	Met	Leu	Ile	Ala 255	His
Leu	Gln	Asp	Lys 260	Phe	Pro	Asp	Туг	Leu 265	Thr	Val	Ser	Pro	Pro 270	Ile	Gly
Asp	Leu	Gln 275	Val	Phe	Tyr	Lys	Glu 280	Ser	Lys	Lys	Arg	Phe 285	Asp	Thr	Glu
Glu	Glu 290	Phe	Lys	Lys	Arg	Ala 295	Tyr	Gln	Cys	Val	Val 300	Leu	Leu	Gln	Gly
Lys 305	Asn	Pro	Asp	Ile	Thr 310	Lys	Ala	Trp	Lys	Leu 315	Ile	Cys	Asp	Val	Ser 320
Arg	Gln	Glu	Leu	Asn 325	Lys	Ile	Tyr	Asp	Ala 330	Leu	Asp	Val	Ser	Leu 335	Ile
Glu	Arg	Gly	Glu 340	Ser	Phe	Tyr	Gln	Asp 345	Arg	Met	Asn	Asp	Ile 350	Val	Lys
Glu	Phe	Glu	Asp	Ara	Glv	Phe	Val	Gln	Val	Asp	Asp	Glv	Ara	Lvs	Ile

		355					300					303			
Val	Phe 370	Val	Pro	Gly	Cys	Ser 375	Ile	Pro	Leu	Thr	Ile 380	Val	Lys	Ser	Asp
Gly 385	Gly	Tyr	Thr	Tyr	Asp 390	Thr	Ser	Asp	Leu	Ala 395	Ala	Ile	Lys	Gln	Arg 400
Leu	Phe	Glu	Glu	Lys 405	Ala	Asp	Met	Ile	Ile 410	Tyr	Val	Val	Asp	Asn 415	Gly
Gln	Ser	Val	His 420	Phe	Gln	Thr	Ile	Phe 425	Ala	Ala	Ala	Gln	Met 430	Ile	Gly
Trp	Туr	Asp 435	Pro	Lys	Val	Thr	Arg 440	Val	Phe	His	Ala	Gly 445	Phe	Gly	Val
Val	Leu 450	Gly	Glu	Asp	Lys	Lys 455	Lys	Phe	Lys	Thr	Arg 460	Ser	Gly	Glu	Thr
Val 465	Arg	Leu	Met	Asp	Leu 470	Leu	Gly	Glu	Gly	Leu 475	Lys	Arg	Ser	Met	Asp 480
Lys	Leu	Lys	Glu	Lys 485	Glu	Arg	Asp	Lys	Val 490	Leu	Thr	Ala	Glu	Glu 495	Leu
Asn	Ala	Ala	Gln 500	Thr	Ser	Val	Ala	туr 505	Gly	Cys	Ile	Lys	Tyr 510	Ala	Asp
Leu	Ser	His 515	Asn	Arg	Leu	Asn	Asp 520	Tyr	Ile	Phe	Ser	Phe 525	Asp	Lys	Met
Leu	Asp 530	Asp	Arg	Gly	Asn	Thr 535	Ala	Ala	Tyr	Leu	Leu 540	Tyr	Ala	Phe	Thr
Arg 545	Ile	Arg	Ser	Ile	Ala 550	Arg	Leu	Ala	Asn	11e 555	Asp	Glu	Glu	Met	Leu 560
Gln	Lys	Ala	Ala	Arg 565	Glu	Thr	Lys	Ile	Leu 570		Asp	His	Glu	Lys 575	Glu
Trp	Lys	Leu	Gly 580	Arg	Суз	Ile	Leu	Arg 585	Phe	Pro	Glu	Ile	Leu 590	Gln	Lys
Ile	Leu	Asp 595	Asp	Leu	Phe	Leu	His 600	Thr	Leu	Cys	Asp	Туг 605	Ile	Tyr	Glu
Leu	Ala 610	Thr	Ala	Phe	Thr	Glu 615	Phe	Tyr	Asp	Ser	Cys 620	Tyr	Cys	Val	Glu
Lys	Asp	Arg	Gln	Thr	Gly	Lys	Ile	Leu	Lys	Val	Asn	Met	Trp	Arg	Met

625 630 635 640

Leu Leu Cys Glu Ala Val Ala Val Met Ala Lys Gly Phe Asp Ile 645 650 655

Leu Gly Ile Lys Pro Val Gln Arg Met
660 665

<210> 594

<211> 116

<212> PRT

<213> Homo sapiens

<400> 594

Thr Val Thr Glu Thr Thr Val Thr Val Thr Glu Pro Glu Asn Arg

1 5 10 15

Ser Leu Thr Ile Lys Leu Arg Lys Arg Lys Pro Glu Lys Lys Val Glu 20 25 30

Trp Thr Ser Asp Thr Val Asp Asn Glu His Met Gly Arg Arg Ser Ser 35 40 45

Lys Cys Cys Cys Ile Tyr Glu Lys Pro Arg Ala Phe Gly Glu Ser Ser 50 60

Thr Glu Ser Asp Glu Glu Glu Glu Gly Cys Gly His Thr His Cys
65 70 75 80

Val Arg Gly His Arg Lys Gly Arg Arg Arg Ala Thr Leu Gly Pro Thr 85 90 95

Pro Thr Thr Pro Pro Gln Pro Pro Asp Pro Ser Gln Pro Pro Pro Gly 100 105 110

Pro Met Gln His 115

<210> 595

<211> 294

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (269)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<22	1> S	TTE													
	2> (
			ona l	e an	v of	the	nat	ural	א מו	ccur	ring	L-a	nino	acio	ds
	J	u u 0	quu.	J 4	, 01				-, 0						
<40	0> 5	95													
	_		Ara	t/a l	Ser	Glu	Ara	Glu	Glv	Pro	Gly	Asn	Pro	Gln	Arc
	GIII	Leu	ALG		261	Giu	n. y	GIU		rio	Gry	пэр	110	15	****
1				5					10					1,	
5 1	.	_					m>		•	•	01	•	3	D	C1 .
Pne	ser	Asp		Thr	Leu	Arg	Thr		Arg	reu	Glu	Asp		PIO	GIÀ
			20					25					30		
	/													_	
Asp	Ala	Met	Trp	Gly	Glu	Gly		Arg	Ala	Trp	Cys		Phe	Val	Glu
		35					40					45			
Asn	Arg	Trp	Cys	Leu	Lys	Arg	Val	Ser	Ala	Pro	Leu	His	Leu	Gly	Let
	50					55					60				
Leu	Gly	Cys	Pro	Asp	Ala	Glu	Ala	His	Phe	Pro	Ala	Met	Leu	Thr	Let
65					70					75					80
Pro	Leu	Ser	Pro	Pro	Ser	Arq	Lys	Met	Ala	Thr	Asn	Phe	Leu	Ala	His
				85		•	•		90					95	
Glu	T.vs	Tle	Tro	Phe	Asp	Lvs	Phe	Lvs	Tur	Asp	Asp	Ala	Glu	Ara	Arc
	2,0		100	1		_,_		105	-1-				110		5
			100					103					110		
Dha		C111	Gla	Mot) en	Gly	Bro	17 - 1	בומ	Gly	Ala	Ser	Ara	Gln	Glu
FIIE	ıyı	115	GIII	nec	VOII	GIY	120	Val	VIG	Gly	лта	125	nry	GIII	GIU
		113					120					123			
	۵,		_		- 1		_		-1-				•	a 1	•
Asn	-	Ala	ser	vaı	ile		Arg	Asp	ıте	Ala	Arg	Ala	Arg	GIU	ASI
	130					135					140				
												_			
Ile	Gln	Lys	Ser	Leu	Ala	Gly	Ser	Ser	Gly	Pro	Gly	Ala	Ser	Ser	
145					150					155					160
Thr	Ser	Gly	Asp	His	Gly	Glu	Leu	Val	Val	Arg	Ile	Ala	Ser	Leu	Glu
				165					170					175	
Val	Glu	Asn	Gln	Ser	Leu	Arg	Gly	Val	Val	Gln	Glu	Leu	Gln	Gln	Ala
			180				_	185					190		
Ile	Ser	Lvs	Leu	Glu	Ala	Ara	Leu	Asn	Val	Leu	Glu	Lvs	Ser	Ser	Pro
		195				•••- 5	200					205			
		175					200					203			
C1	u; ~	h	- נת	mh	21-	D	C1-	mh	C1 =	u: -	17-1	e	Dro	Mot	λ
GTÀ		wid	wig	TILL	Ald		GIU	THE	GIII	nis	Val	oer	LIO	rie C	wr 3
	210					215					220				
~1 ·	***	03	D	D	N 7 -	.	. .	-		m\	D == =	. 1 -	61		
	val	GIU	Pro	PTO		гàг	гÀг	Pro	Ala		Pro	ΑΙΑ	GIU	Asp	_
225					230					235					240

Glu Asp Asp Ile Asp Leu Phe Gly Ser Asp Asn Glu Glu Asp 245 250 255

Lys Glu Ala Ala Gln Leu Arg Glu Glu Arg Leu Arg Xaa Tyr Ala Glu 260 265 270

Lys Lys Ala Lys Lys Xaa Ala Leu Val Ala Lys Ser Ser Ile Leu Leu 275 280 285

Asp Phe Lys Pro Trp Gly 290

<210> 596

<211> 134

<212> PRT

<213> Homo sapiens

<400> 596

Val Ser Arg Leu Gly Leu Leu Thr Pro Leu Gly Cys Ser Phe Gly Thr

Asp Glu Trp Leu Cys Pro Val Thr Ala Leu Ser Leu Pro Gly Gly Tyr
20 25 30

Val His Ser Arg Pro Leu Pro Arg Leu Arg Pro Met Arg Tyr Gly Asp 35 40 45

Thr Leu Ala Pro Arg Ser Trp Arg His Arg Pro Leu Pro Trp His Ser 50 55 60

Ser Phe Ala Gly Asp Pro Pro Leu Pro Lys Ala Leu Ser Pro Cys Ser 65 70 75 80

His Ser Arg Arg Thr Ala Ala Arg Ala Ser Gly Ser Leu Ala Thr Gly 85 90 95

Phe Glu Arg Leu His Ser Trp Gly Leu Glu Gly Gly Val Pro Lys Ala 100 105 110

Leu Ser Lys Ser Gln Ser Ser Ser His Gln Ser Leu Tyr Lys Val Leu 115 120 125

Gly Pro Glu Ala Leu Pro 130

<210> 597

PCT/US00/05881 WO 00/55173

555

<211> 91

<212> PRT

<213> Homo sapiens

<400> 597

Glu Gly Pro Glu Gly Ala Asn Leu Phe Ile Tyr His Leu Pro Gln Glu 10

Phe Gly Asp Gln Asp Ile Leu Gln Met Phe Met Pro Phe Gly Asn Val

Ile Ser Ala Lys Val Phe Ile Asp Lys Gln Thr Asn Leu Ser Lys Cys

Phe Gly Phe Val Ser Tyr Asp Asn Pro Val Ser Ala Gln Ala Ala Ile

Gln Ala Met Asn Gly Phe Gln Ile Gly Met Lys Arg Leu Lys Val Gln 70 75

Leu Lys Arg Ser Lys Asn Asp Ser Lys Pro Tyr

<210> 598

<211> 68

<212> PRT

<213> Homo sapiens

Arg Pro Thr Arg Pro Glu Lys Val Gly Ser Gly Gly Ser Ser Val Gly 10 5

Ser Gly Asp Ala Ser Ser Ser Arg His His His Arg Arg Arg Phe 25

His Leu Pro Gln Gln Pro Leu Leu Gln Arg Glu Val Trp Cys Val Gly 35

Thr Thr Gly Asn Ala Asn Gln Ala Gln Ser Ser Thr Glu Gln Thr Leu . 50 55

Leu Lys Pro Lys

<210> 599

<211> 119

<212> PRT

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<213> Homo sapiens
<220>
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<222> (58)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
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<222> (68)
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<220>
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<222> (98)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
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<222> (99)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 599
Phe Gly Arg Asp Gln Val Tyr Leu Ser Tyr Asn Asn Val Ser Ser Leu
                  5
 1
                                     10
Lys Met Leu Val Ala Lys Asp Asn Trp Val Leu Ser Ser Glu Ile Ser
             20
                                 25
Gln Val Arg Leu Tyr Thr Leu Glu Asp Asp Lys Phe Leu Ser Phe His
                             40
Met Glu Met Val Val His Val Asp Ala Xaa Gln Ala Phe Leu Leu
     50
                         55
                                             60
Ser Asp Leu Xaa Gln Arg Pro Glu Trp Asp Lys His Tyr Arg Ser Val
                     70
                                         75
Glu Leu Val Gln Gln Val Asp Xaa Gly Arg Arg His Leu Pro Arg His
                                     90
Gln Xaa Xaa Pro Arg Arg Ser His Lys Ala Pro Gly Leu Arg Asp Pro
            100
                                105
Gly Leu Glu Ala Glu Ala Leu
       115
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<210> 600
<211> 177
<212> PRT
<213> Homo sapiens
<220>
<221> SITE
<222> (1)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (8)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (69)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (135)
<223> Xaa equals any of the naturally occurring L-amino acids
Xaa Glu Arg Leu Arg Ala Gln Xaa Glu Lys Ser Arg Asp Ser Gln Pro
Arg Leu Pro Leu Arg Phe Pro Ser Trp Arg Gly Pro Trp Cys Gly Ile
                                 25
Glu Ile Ala Gly Tyr Gly Ala Glu Val Phe Arg Gln Tyr Trp Asp Ile
Pro Asp Gly Thr Asp Cys His Arg Lys Ala Tyr Ser Thr Thr Ser Ile
Ala Ser Val Ala Xaa Leu Thr Ala Ala Ala Tyr Arg Val Thr Leu Asn
                                         75
Pro Pro Gly Thr Phe Leu Glu Gly Val Ala Lys Val Gly Gln Tyr Thr
                 85
                                     90
Phe Thr Ala Ala Ala Val Gly Ala Val Phe Gly Leu Thr Thr Cys Ile
                                105
Ser Ala His Val Arg Glu Lys Pro Asp Asp Pro Leu Asn Tyr Phe Leu
```

558

120 125 115 Gly Gly Cys Ala Gly Gly Xaa Thr Leu Gly Ala Arg Thr His Asn Tyr 135 130 Gly Ile Gly Ala Ala Ala Cys Val Tyr Phe Gly Ile Ala Ala Ser Leu 150 155 Val Lys Met Gly Arg Leu Glu Gly Trp Glu Val Phe Ala Lys Pro Lys 170 Val <210> 601 <211> 218 <212> PRT <213> Homo sapiens Arg Gly Gly Gly Gly Ala Ser Ser Cys Cys Cys Ala Pro Ser 5 10 Pro Arg Gly Arg Pro Val Pro Ala Arg Thr Pro Arg Arg Cys Pro Arg 25 Pro Ser Pro Gly Pro Ala Met Gly Leu Thr Val Ser Ala Leu Phe Ser 35 40 Arg Ile Phe Gly Lys Lys Gln Met Arg Ile Leu Met Val Gly Leu Asp . 55 Ala Ala Gly Lys Thr Thr Ile Leu Tyr Lys Leu Lys Leu Gly Glu Ile 70 Val Thr Thr Ile Pro Thr Ile Gly Phe Asn Val Glu Thr Val Glu Tyr 90 Lys Asn Ile Cys Phe Thr Val Trp Asp Val Gly Gln Asp Lys Ile 100 105 Arg Pro Leu Trp Arg His Tyr Phe Gln Asn Thr Gln Gly Leu Ile Phe 120 125 Val Val Asp Ser Asn Asp Arg Glu Arg Val Gln Glu Ser Ala Asp Glu 130 135

Leu Gln Lys Met Leu Gln Glu Asp Glu Leu Arg Asp Ala Val Leu Leu

155

Val Phe Ala Asn Lys Gln Asp Met Pro Asn Ala Met Pro Val Ser Glu 165 170 175

Leu Thr Asp Lys Leu Gly Leu Gln His Leu Arg Ser Arg Thr Trp Tyr 180 185 190

Val Gln Ala Thr Cys Ala Thr Gln Gly Thr Gly Leu Tyr Asp Gly Leu 195 200 205

Asp Trp Leu Ser His Glu Leu Ser Lys Arg 210 215

<210> 602

<211> 829

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (32)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (454)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 602

Pro Gly Gln Ala Gly Ala Glu Gly His Val Arg Cys Cys Pro Gly Glu
1 5 10 15

Glu Gln Lys Ala Gly Glu Glu Arg Arg Cys Pro Gly Pro Gln Arg Xaa 20 25 30

Gly Ala Ala Leu Gly Pro Gly Pro Gly Glu Ala Arg Leu Asp Tyr Ser 35 40 45

Glu Phe Phe Thr Glu Asp Val Gly Gln Leu Pro Gly Leu Thr Ile Trp 50 55 60

Gln Ile Glu Asn Phe Val Pro Val Leu Val Glu Glu Ala Phe His Gly 65 70 75 80

Lys Phe Tyr Glu Ala Asp Cys Tyr Ile Val Leu Lys Thr Phe Leu Asp 85 90 95

Asp Ser Gly Ser Leu Asn Trp Glu Ile Tyr Tyr Trp Ile Gly Glu 100 105 110

VIG	1111	115	vah	Буз	Буз	ALG	120	361	AIA	116	1113	125	var	non	
Arg	Asn 130	Tyr	Leu	Gly	Ala	Glu 135	Суз	Arg	Thr	Val	Arg 140	Glu	Glu	Met	Gly
Asp 145	Glu	Ser	Glu	Glu	Phe 150	Leu	Gln	Val	Phe	Asp 155	Asn	Asp	Ile	Ser	Tyr 160
Ile	Glu	Gly	Gly	Thr 165	Ala	Ser	Gly	Phe	Tyr 170	Thr	Val	Glu	Asp	Thr 175	His
Tyr	Val	Thr	Arg 180	Met	Tyr	Arg	Val	Туг 185	Gly	Lys	Lys	Asn	11e 190	Lys	Leu
Glu	Pro	Val 195	Pro	Leu	Lys	Gly	Thr 200	Ser	Leu	Asp	Pro	Arg 205	Phe	Val	Phe
	210	_				215					220			Gln	
Thr 225	Leu	Ser	Ser	Thr	Thr 230	Lys	Ala	Arg	Leu	Phe 235	Ala	Glu	Lys	Ile	Asn 240
Lys	Asn	Glu		Lys 245	Gly	Lys	Ala	Glu	Ile 250	Thr	Leu	Leu	Val	Gln 255	Gly
Gln	Glu	Leu	Pro 260	Glu	Phe	Trp	Glu	Ala 265	Leu	Gly	Gly	Glu	Pro 270	Ser	Glu
	-	275					280					285		Lys	
_	290					295					300			Ile	
305	-				310					315				Leu	320
	-			325					330	-			-	Val 335	
			340					345					350	Lys	
		355					360					365		Leu	
Gly	Met 370	Leu	His	Arg	Pro	Arg 375	His	Ala	Thr	Val	Ser 380	Arg	Ser	Leu	Glu

385	Tnr	GIU	AIA	Gin	390	Pne	гуѕ	АТА	гуз	395	гÀг	ASII	110	wsb	400
Val	Leu	Thr	Val	Asp 405	Tyr	Thr	Arg	Asn	Ala 410	Glu	Ala	Val	Leu	Gln 415	Ser
Pro	Gly	Leu	Ser 420	Gly	Lys	Val	Lys	Arg 425	Asp	Ala	Glu	Lys	Lys 430	Asp	Gln
Met	Lys	Ala 435	Asp	Leu	Thr	Ala	Leu 440	Phe	Leu	Pro	Arg	Gln 445	Pro	Pro	Met
Ser	Leu 450	Ala	Glu	Ala	Xaa	Gln 455	Leu	Met	Glu	Glu	Trp 460	Asn	Glu	Asp	Leu
Asp 465	_	Met	Glu	Gly	Phe 470	Val	Leu	Glu	Gly	Lys 475	Lys	Phe	Ala	Arg	Leu 480
Pro	Glu	Glu	Glu	Phe 485	Gly	His	Phe	Tyr	Thr 490	Gln	Asp	Cys	Tyr	Val 495	Phe
Leu	Суз	Arg	Tyr 500	Trp	Val	Pro	Val	Glu 505	Tyr	Glu	;Glu	Glu	Glu 510	Lys	Lys
		515			Lys		520					525			
	530				Lys	535					540				
545		-		•	Arg 550					555					560
Thr	Phe	Ser	Leu	Gln 565	Lys	Lys	Phe	Glu	Ser 570	Leu	Phe	Pro	Gly	Lys 575	Leu
			580		Thr			585					590		
		595			Phe		600					605			
Gln	Gly 610	Ala	Gln	Gln	Pro	Ser 615	Leu	Tyr	Gln	Ile	Arg 620	Thr	Asn	Gly	Ser
625	٠	-			Cys 630					635					640
Asn	Ser	Glu	Phe	Cys 645	Phe	Ile	Leu	Lys	Val 650	Pro	Phe	Glu	Ser	Glu 655	Asp

PCT/US00/05881 WO 00/55173

562

Asn Gln Gly Ile Val Tyr Ala Trp Val Gly Arg Ala Ser Asp Pro Asp 665 Glu Ala Lys Leu Ala Glu Asp Ile Leu Asn Thr Met Phe Asp Thr Ser 675 680 Tyr Ser Lys Gln Val Ile Asn Glu Glu Glu Pro Glu Asn Phe Phe Trp Val Gly Ile Gly Ala Gln Lys Pro Tyr Asp Asp Asp Ala Glu Tyr 710 715 720 Met Lys His Thr Arg Leu Phe Arg Cys Ser Asn Glu Lys Gly Tyr Phe 725 Ala Val Thr Glu Lys Cys Ser Asp Phe Cys Gln Asp Asp Leu Ala Asp 745 Asp Asp Ile Met Leu Leu Asp Asn Gly Gln Glu Val Tyr Met Trp Val 760 Gly Thr Gln Thr Ser Gln Val Glu Ile Lys Leu Ser Leu Lys Ala Cys 775 Gln Val Tyr Ile Gln His Met Arg Ser Lys Glu His Glu Arg Pro Arg 790 795 Arg Leu Arg Leu Val Arg Lys Gly Asn Glu Gln His Ala Phe Thr Arg 805 810 Cys Phe His Ala Trp Ser Ala Phe Cys Lys Ala Leu Ala

<210> 603

<211> 221

<212> PRT

<213> Homo sapiens

<400> 603

Thr Glu Pro Pro Leu Ser Cys Cys Leu Pro Ala Thr Tyr Pro Ala Asp

Met Gly Thr Ala Gly Ala Met Gln Leu Cys Trp Val Ile Leu Gly Phe 25

Leu Leu Phe Arg Gly His Asn Ser Gln Pro Thr Met Thr Gln Thr Ser 35 40

<210> 604

<211> 97

<212> PRT

<213> Homo sapiens

<400> 604

Ser Cys Gly Leu Ser Leu Ile Lys Met Thr Thr Ser Gln Lys His Arg

Asn Asn Gly Lys Gln Ser Leu Ser Ala Glu Lys Val Leu

Asp Phe Val Ala Glu Pro Met Gly Glu Lys Pro Val Gly Ser Leu Ala 20 25 30

Gly Ile Gly Glu Val Leu Gly Lys Lys Leu Glu Glu Arg Gly Phe Asp $35 \hspace{1cm} 40 \hspace{1cm} 45$

Lys Ala Tyr Val Val Leu Gly Gln Phe Leu Val Leu Lys Lys Asp Glu

55 50 60

Asp Leu Phe Arg Glu Trp Leu Lys Asp Thr Cys Gly Ala Asn Ala Lys 70

Gln Ser Arg Asp Cys Phe Gly Cys Leu Arg Glu Trp Cys Asp Ala Phe

Leu

<210> 605

<211> 266

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (84)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 605

Gly Pro Arg Arg Leu Gly Ala Leu His Ala Ala Ala Thr Gly Ala Arg

Cys Leu Val Glu Leu Leu Val Ala His Gly Ala Asp Leu Asn Ala Lys 25

Ser Leu Met Asp Glu Thr Pro Leu Asp Val Cys Gly Asp Glu Glu Val

Arg Ala Lys Leu Leu Glu Leu Lys His Lys His Asp Ala Leu Leu Arg . 55

Ala Gln Ser Arg Gln Arg Ser Leu Leu Arg Arg Arg Thr Ser Ser Ala

Gly Ser Arg Xaa Lys Val Val Arg Arg Val Ser Leu Thr Gln Arg Thr 85 90

Asp Leu Tyr Arg Lys Gln His Ala Gln Glu Ala Ile Val Trp Gln Gln 100

Pro Pro Pro Thr Ser Pro Glu Pro Pro Glu Asp Asn Asp Asp Arg Gln 120

Thr Gly Ala Glu Leu Arg Pro Pro Pro Pro Glu Glu Asp Asn Pro Glu 130 135

Val Val Arg Pro His Asn Gly Arg Val Gly Gly Ser Pro Val Arg His 150 155 Leu Tyr Ser Lys Arg Leu Asp Arg Ser Val Ser Tyr Gln Leu Ser Pro Leu Asp Ser Thr Thr Pro His Thr Leu Val His Asp Lys Ala His His 180 Thr Leu Ala Asp Leu Lys Arg Gln Arg Ala Ala Lys Leu Gln Arg Pro Pro Pro Glu Gly Pro Glu Ser Pro Glu Thr Ala Glu Pro Gly Leu Pro Gly Asp Thr Val Thr Pro Gln Pro Asp Cys Gly Phe Arg Ala Gly Gly Asp Pro Pro Leu Leu Lys Leu Thr Ala Pro Ala Val Glu Ala Pro 250 Val Glu Arg Arg Pro Cys Cys Leu Leu Met <210> 606 <211> 331 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (91) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (285) <223> Xaa equals any of the naturally occurring L-amino acids His Asp Ser Cys Phe Val Glu Met Gln Ala Gln Lys Val Met His Val Ser Ser Ala Glu Leu Asn Tyr Ser Leu Pro Tyr Asp Ser Lys His Gln 25 Ile Arg Asn Ala Ser Asn Val Lys His His Asp Ser Ser Ala Leu Gly

40

Vul	50	501	-1-	110		55	V 41	GIU	ASII	110	60		501	552	
Pro 65	Pro	Ser	Gly	Thr	Ser 70	Ser	Lys	Met	Ser	Leu 75	Asp	Leu	Pro	Glu	Lys 80
Gln	Asp	Gly	Thr	Val 85	Phe	Pro	Ser	Ser	Leu 90	Xaa	Pro	Thr	Ser	Ser 95\	
Ser	Leu	Phe	Ser 100	Tyr	Tyr	Asn	Ser	His 105	Asp	Ser	Leu	Ser	Leu 110	Asn	Ser
Pro	Thr	Asn 115	Ile	Ser	Ser	Leu	Leu 120	Asn	Gln	Glu	Ser	Ala 125	Val	Leu	Ala
Thr	Ala 130	Pro	Arg	Ile	Asp	Asp 135	Glu	Ile	Pro	Pro	Pro 140	Leu	Pro	Val	Arg
145					150					155				Ser	160
Asn	Val	Pro	Lys	Ser 165	Leu	Ser	Ser	Ala	Val 170	Lys	Val	Lys	Ile	Gly 175	Thr
			180					185					190	Asp	
		195					200					205	,	Lys	
	210					215					220			Glu	
225					230					235				Ala	240
				245					250					Asn 255	
			260					265					270	Thr	
		275					280					285		Cys	
	290					295	·				300			Asn	
Ser 305	Ser	Phe	Leu	Asn	Phe 310	Gly	Phe	Ala	Asn	Arg 315	Phe	Ser	Lys	Pro	Lys 320

Gly Pro Arg Asn Pro Pro Pro Thr Trp Asn Ile 325

<210> 607

<211> 192

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (78)

<223> Xaa equals any of the naturally occurring L-amino acids

Ala Ala Pro Ser Glu Pro Lys Ala Arg Gly Gly His Gly Gly Ala Leu 10

Ala Arg Leu Glu Thr Met Pro Lys Leu Gln Gly Phe Glu Phe Trp Ser 25

Arg Thr Leu Arg Gly Ala Arg His Val Val Ala Pro Met Val Asp Gln

Ser Glu Leu Ala Trp Arg Leu Leu Ser Arg Arg His Gly Ala Gln Leu

Cys Tyr Thr Pro Met Leu His Ala Gln Val Phe Val Arg Xaa Ala Asn 75 70

Tyr Arg Lys Glu Asn Leu Tyr Cys Glu Val Cys Pro Glu Asp Arg Pro

Leu Ile Val Gln Phe Cys Ala Asn Asp Pro Glu Val Phe Val Gln Ala 105

Ala Leu Leu Ala Gln Asp Tyr Cys Asp Ala Ile Asp Leu Asn Leu Gly

Cys Pro Gln Met Ile Ala Lys Arg Gly His Tyr Gly Ala Phe Leu Gln 135

Asp Glu Trp Asp Leu Leu Gln Arg Met Ile Leu Leu Ala His Glu Lys 155

Leu Ser Val Pro Val Thr Cys Lys Ile Arg Val Phe Pro Glu Ile Asp 165 170

Lys Thr Val Ser Thr Pro Arg Cys Trp Arg Arg Pro Ala Ala Ser Cys 180 185

<213 <213	0> 60 1> 4: 2> PI 3> Ho	15 RT	sapie	ens							,				
<400	0> 60	80													
His 1	Ile	Lys	Cys	Pro 5	His	Ser	Lys	Tyr	Gly 10	Cys	Thr	Phe	Ile	Gly 15	Asn
Gln	Asp	Thr	Tyr 20	Glu	Thr	His	Leu	Glu 25	Thr	Cys	Arg	Phe	Glu 30	Gly	Leu
Lys	Glu	Phe 35	Leu	Gln	Gln	Thr	Asp 40	Asp	Arg	Phe	His	Glu 45	Met	His	Val
Ala	Leu 50	Ala	Gln	Lys	Asp	Gln 55	Glu	Ile	Ala	Phe	Leu 60	Arg	Ser	Met	Leu
Gly 65	Lys	Leu	Ser	Glu	Lys 70	Ile	Asp	Gln	Leu	Glu 75	Lys	Ser	Leu	Glu	Leu 80
Lys	Phe	Asp	Val	Leu 85	Asp	Glu	Asn	Gln	Ser 90	Lys	Leu	Ser	Glu	Asp 95	Leu
Met	Glu	Phe	Arg 100	Arg	Asp	Ala	Ser	Met 105	Leu	Asn	Asp	Glu	Leu 110	Ser	His
Ile	Asn	Ala 115	Arg	Leu	Asn	Met	Gly 120	Ile	Leu	Gly	Ser	Tyr 125	Asp	Pro	Gln
Gln	Ile 130	Phe	Lys	Cys	Lys	Gly 135	Thr	Phe	Val	Gly	His 140	Gln	Gly	Pro	Val
Trp 145	Cys	Leu	Cys	Val	Tyr 150	Ser	Met	Gly	Asp	Leu 155	Leu	Phe	Ser	Gly	Ser 160
Ser	Asp	Lys	Thr	Ile 165	Lys	Val	Trp	Asp	Thr 170	Cys	Thr	Thr	Tyr	Lys 175	Cys
Gln	Lys	Thr	Leu 180	Glu	Gly	His	Asp	Gly 185	Ile	Val	Leu	Ala	Leu 190	Cys	Ile
Gln	Gly	Cys 195	Lys	Leu	Tyr	Ser	Gly 200	Ser	Ala	Asp	Cys	Thr 205	Ile	Ile	Val

)

Trp Asp Ile Gln Asn Leu Gln Lys Val Asn Thr Ile Arg Ala His Asp 215 Asn Pro Val Cys Thr Leu Val Ser Ser His Asn Val Leu Phe Ser Gly Ser Leu Lys Ala Ile Lys Val Trp Asp Ile Val Gly Thr Glu Leu Lys 250 Leu Lys Lys Glu Leu Thr Gly Leu Asn His Trp Val Arg Ala Leu Val 260 Ala Ala Gln Ser Tyr Leu Tyr Ser Gly Ser Tyr Gln Thr Ile Lys Ile Trp Asp Ile Arg Thr Leu Asp Cys Ile His Val Leu Gln Thr Ser Gly 295 Gly Ser Val Tyr Ser Ile Ala Val Thr Asn His His Ile Val Cys Gly 315 Thr Tyr Glu Asn Leu Ile His Val Trp Asp Ile Glu Ser Lys Glu Gln Val Arg Thr Leu Thr Gly His Val Gly Thr Val Tyr Ala Leu Ala Val Ile Ser Thr Pro Asp Gln Thr Lys Val Phe Ser Ala Ser Tyr Asp Arg 360 Ser Leu Arg Val Trp Ser Met Asp Asn Met Ile Cys Thr Gln Thr Leu 375 Leu Arg His Gln Gly Ser Val Thr Ala Leu Ala Val Ser Arg Gly Arg 385 390 Leu Phe Ser Gly Ala Val Asp Ser Thr Val Lys Val Trp Thr Cys 405 410

<210> 609

<211> 48

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (27)

<223> Xaa equals any of the naturally occurring L-amino acids

PCT/US00/05881 WO 00/55173

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<220>
<221> SITE
<222> (34)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 609
Phe Ser Glu Leu Asn Gln Cys Phe Tyr Ile Cys Phe Phe Phe Tyr Ala
                                    10
Ser Trp Lys Trp Arg Met Lys Ile Gln Leu Xaa Cys Ser Asn Ser Arg
                                 25
Arg Xaa Val Ser Thr Glu Lys Gly Thr Cys Phe Phe Thr Pro Glu Leu
                             40
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<210> 610
<211> 241
<212> PRT
<213> Homo sapiens
<220>
<221> SITE
<222> (1)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (3)
<223> Xaa equals any of the naturally occurring L-amino acids
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<222> (7)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
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<222> (13)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (37)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 610
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PCT/US00/05881

Xaa 1	Asp	Xaa	Gly	Arg 5	Pro	Xaa	Arg	Thr	Ala 10	Glu	Ser	Xaa	Phe	Gly 15	Ile
Asn	Leu	Lys	Gly 20	Pro	Lys	Ile	Lys	Gly 25	Gly	Ala	Asp	Val	Ser 30	Gly	Gly
Val	Ser	Ala 35	Pro	Xaa	Ile	Ser	Leu 40	Gly	Glu	Gly	His	Leu 45	Ser	Val	Lys
Gly	Ser 50	Gly	Gly	Glu	Trp	Lys 55	Gly	Pro	Gln	Val	Ser 60	Ser	Ala	Leu	Asn
Leu 65	Asp	Thr	Ser	Lys	Phe 70	Ala	Gly	Gly	Leu	His 75	Phe	Ser	Gly	Pro	Eys
Val	Glu	Gly	Gly	Val 85	Lys	Gly	Gly	Gln	Ile 90	Gly	Leu	Gln	Ala	Pro 95	Gly
Leu	Ser	Val	Ser 100	Gly	Pro	Gln	Gly	His 105	Leu	Glu	Ser	Gly	Ser 110	Gly	Lys
Val	Thr	Phe 115	Pro	Lys	Met	Lys	11e 120	Pro	Lys	Phe	Thr	Phe 125	Ser	Gly	Arg
	130		Gly			135					140				
145			Ile		150					155					160
			Leu	165					170					175	
	-		Lys 180	_		_	_	185		-			190		
		195	Ser		_		200					205			
	210		Gly			215					220				
225	Ser	Leu	Phe	Lys	Ser 230	Lys	Lys	Pro	Arg	His 235	Arg	Cys	Lys	Phe	Ile 240
Gln															

<211> 77

<212> PRT

<213> Homo sapiens

<400> 611

His Tyr Arg Arg Tyr Ala Cys Arg Tyr Arg Ser Gly Ile Pro Gly Ser

Thr His Ala Ser Gly Val Ala Asp Gly Gly Gln Val Phe Leu Phe Pro 25

Glu Thr Gly Ser Val Gln Thr Ala Asn Ala His Arg Trp Pro Arg Gly

Gly Gly Ser Gln Gly Val Trp Val Phe Leu Gly Phe Phe Ser Val Val

Ser Phe Thr Gln Gly Trp Trp Ser Gln Pro Val Trp Cys 70

<210> 612

<211> 137

<212> PRT

<213> Homo sapiens

<400> 612

Leu Gln Val Pro Val Arg Asn Ser Gly Ser Pro Thr Arg Gln Ala Ala 1 5

Ala Met Thr Phe Cys Arg Leu Leu Asn Arg Cys Gly Glu Ala Ala Arg

Ser Leu Pro Leu Gly Ala Arg Cys Phe Gly Val Arg Val Ser Pro Thr

Gly Glu Lys Val Thr His Thr Gly Gln Val Tyr Asp Asp Lys Asp Tyr

Arg Arg Ile Arg Phe Val Gly Arg Gln Lys Glu Val Asn Glu Asn Phe

Ala Ile Asp Leu Ile Ala Glu Gln Pro Val Ser Glu Val Glu Thr Arg

Val Ile Ala Cys Asp Gly Gly Gly Ala Leu Gly His Pro Lys Val 100

Tyr Ile Asn Leu Asp Lys Glu Thr Lys Thr Gly Thr Cys Gly Tyr Cys 120

573

Gly Leu Gln Phe Arg Gln His His His 130 135

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<210> 613
<211> 122
<212> PRT
<213> Homo sapiens
<220>
<221> SITE
<222> (50)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (75)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
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<222> (80)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
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<222> (85)
<223> Xaa equals any of the naturally occurring L-amino acids
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<222> (98)
<223> Xaa equals any of the naturally occurring L-amino acids
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<222> (105)
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<220>
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<222> (111)
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<220>
<221> SITE
<222> (116)
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<223> Xaa equals any of the naturally occurring L-amino acids

<400> 613

Tyr Ser Thr Asp Asn Asn Asn Trp Tyr Ser Ile Phe Tyr Leu His

1 5 10 15

Ser Ser Phe Leu Gly Glu Asn Ala Glu Lys Leu Leu Gln Phe Lys Arg 20 25 30

Trp Phe Trp Ser Ile Val Glu Lys Met Ser Met Thr Glu Arg Gln Asp
35 40 45

Leu Xaa Tyr Phe Trp Thr Ser Ser Pro Ser Leu Pro Ala Ser Glu Glu 50 55 60

Gly Phe Gln Pro Met Pro Ser Ile Thr Ile Xaa Pro Pro Asp Asp Xaa 65 70 75 80

His Leu Pro Thr Xaa Lys Tyr Leu His Phe Leu Asp Phe Thr Phe Pro 85 90 95

Leu Xaa Ser Phe Lys Gln Asp Ser Xaa Asn Arg Lys Leu Val Xaa Ser 100 105 110

Pro Phe Arg Xaa Gln Lys Phe Trp Val Leu 115 120

<210> 614

<211> 62

<212> PRT

<213> Homo sapiens

<400> 614

Phe Phe Ile Gly Leu Glu Thr Arg Ala Asn Ser Ile Met Phe Ser Lys
1 10 15

Glu Thr Asp Leu Ser Cys Trp Ile Arg Gly Thr Asn Pro Thr Tyr Met
20 25 30

Ile Phe Phe Leu Phe Leu Ser Cys Ser Tyr Gly Thr Val Leu Phe Gly 35 40 45

Thr Phe Ala Thr Arg Asp Asn Thr Thr Phe Leu Thr Leu Ile 50 55 60

<210> 615

<211> 159

<212> PRT

<213> Homo sapiens

<400> 615 Val Gly Leu Pro Asn Met Ala Gln Ser Ile Asn Ile Thr Glu Leu Asn Leu Pro Gln Leu Glu Met Leu Lys Asn Gln Leu Asp Gln Glu Val Glu Phe Leu Ser Thr Ser Ile Ala Gln Leu Lys Val Val Gln Thr Lys Tyr Val Glu Ala Lys Asp Cys Leu Asn Val Leu Asn Lys Ser Asn Glu Gly Lys Glu Leu Leu Val Pro Leu Thr Ser Ser Met Tyr Val Pro Gly Lys Leu His Asp Val Glu His Val Leu Ile Asp Val Gly Thr Gly Tyr Tyr 90 Val Glu Lys Thr Ala Glu Asp Ala Lys Asp Phe Phe Lys Arg Lys Ile 105 Asp Phe Leu Thr Lys Gln Met Glu Lys Ile Gln Pro Ala Leu Gln Glu 120 Lys His Ala Met Lys Gln Ala Val Met Glu Met Met Ser Gln Lys Ile 130 135 Gln Gln Leu Thr Ala Leu Gly Ala Ala Gln Ala Thr Ala Lys Ala 150 145 <210> 616 <211> 93 <212> PRT <213> Homo sapiens <220> <221> SITE

<222> (8)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 616
Lys Val Ala Cys Arg Tyr Arg Xaa Gly Ile Pro Gly Arg Pro Thr Arg
1 5 10 15

Pro Gly Thr Gln Asp Ala Glu Gly Lys Lys Ala Lys Gly Lys Lys Val
20 25 30

PCT/US00/05881 WO 00/55173

576

Ala Pro Ala Pro Ala Val Val Lys Lys Gln Glu Ala Lys Lys Val Val 40 35

Asn Pro Leu Phe Glu Lys Arg Pro Lys Asn Phe Gly Ile Gly Gln Asp

Ile Gln Pro Lys Arg Asp Leu Thr Arg Phe Val Lys Trp Pro Arg Tyr 75

Ile Arg Leu Gln Arg His Ala Arg Ser Ser Thr Ser Gly

<210> 617

<211> 362

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (307)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 617

Ser Arg Val Asp Pro Arg Val Arg Arg Gly Val Pro Tyr Gln Leu Gly

Pro His Gly His Arg Gln Gly Leu Glu Ala Pro Leu Tyr Leu Thr Pro

Glu Gly Trp Ser Leu Phe Leu Gln Arg Tyr Tyr Gln Val Wal His Glu 40 35

Gly Ala Glu Leu Arg His Leu Asp Thr Gln Val Gln Arg Cys Glu Asp

Ile Leu Gln Gln Leu Gln Ala Val Pro Gln Ile Asp Met Glu Gly 65

Asp Arg Asn Ile Trp Ile Val Lys Pro Gly Ala Lys Ser Arg Gly Arg

Gly Ile Met Cys Met Asp His Leu Glu Glu Met Leu Lys Leu Val Asn 105

Gly Asn Pro Val Val Met Lys Asp Gly Lys Trp Val Val Gln Lys Tyr 115

Ile Glu Arg Pro Leu Leu Ile Phe Gly Thr Lys Phe Asp Leu Arg Gln 135 130

Trp 145	Phe	Leu	Val	Thr	150	Trp	Asn	Pro	Leu	Thr 155	Val	Trp	Phe	Tyr	Arg 160
Asp	Ser	Tyr	Ile	Arg 165	Phe	Ser	Thr	Gln	Pro 170	Phe	Ser	Leu	Lys	Asn 175	Leu
Asp	Asn	Ser	Val 180	His	Leu	Cys	Asn	Asn 185	Ser	Ile	Gln	Lys	His 190	Leu	Glu
Asn	Ser	Cys 195	His	Arg	His	Pro	Leu 200	Leu	Pro	Pro	Asp	Asn 205	Met	Trp	Ser
Ser	Gln 210	Arg	Phe	Gln	Ala	His 215	Leu	Gln	Glu	Met	Gly 220	Ala	Pro	Asn	Ala
Trp 225	Ser	Thr	Ile	Ile	Val 230	Pro	Gly	Met	Lys	Asp 235	Ala	Val	Ile	His	Ala 240
Leu	Gln	Thr	Ser	Gln 245	Asp	Thr	Val	Gln	Cys 250	Arg	Lys	Ala	Ser	Phe 255	Glu
Leu	Tyr	Gly	Ala 260	Asp	Phe	Val	Phe	Gly 265	Glu	Asp	Phe	Gln	Pro 270	Trp	Leu
Ile	Glu	Ile 275	Asn	Ala	Ser	Pro	Thr 280	Met	Ala	Pro	Ser	Thr 285	Ala	Val	Thr
Ala	Arg 290	Leu	Cys	Ala	Gly	Val 295	Gln	Ala	Asp	Thr	Leu 300	Arg	Val	Val	Ile
305	_				310				Thr	315					320
Tyr	Lys	Gln	Pro	Ala 325	Val	Glu	Val	Pro	Gln 330	Tyr	Val	Gly	Ile	Arg 335	Leu
Leu	Val	Glu	Gly 340	Phe	Thr	Ile	Lys	Lys 345	Pro	Met	Ala	Met	Cys 350	His	Arg
Arg	Met	Gly 355	Val	Arg	Gln	Gln	Ser 360	Leu	Cys						

<210> 618

<211> 328

<212> PRT

<213> Homo sapiens

<400> 618

1	Arg	met	Arg	5	тгр	Trp	vaı	GIN	10	GTÅ	Leu	Leu	AIG	15	PLO
Leu	Leu	Ala	Ala 20	туг	Leu	His	Ile	Pro 25	Pro	Pro	Gln	Leu	Ser 30	Pro	Ala
Leu	His	Ser 35	Trp	Lys	Ser	Ser	Gly 40	Lys	Phe	Phe	Thr	Tyr 45	Lys	Gly	Leu
Arg	Ile 50	Phe	Tyr	Gln	Asp	Ser 55	Val	Gly	Val	Val	Gly 60	Ser	Pro	Glu	Ile
65			Leu		70			,		75					80
	_		Gly	85					90					95	
Phe	Leu	Gly	Phe 100	Gly	Phe	Ser	Asp	Lys 105	Pro	Arg	Pro	His	His 110	Tyr	Ser
		115	Gln				120					125	,		
	130		Arg			135					140				
Val 145	Ala	Gln	Glu	Leu	Leu 150	Tyr	Arg	Tyr	Lys	Gln 155	Asn	Arg	Ser	Gly	Arg 160
			Lys	165		-			170	•	-			175	
			Pro 180					185					190		
		195	Ile			-	200					205			_
	210		Pro			215					220				
225	_	-	Met	_	230	_				235	_	_			240
			Leu	245					250					255	
Arg	Trp	Val	Gly 260	Ala	Leu	Ala	Ser	Val 265	Thr	Ile	Pro	Ile	His 270	Phe	Ile

579

Tyr Gly Pro Leu Asp Pro Val Asn Pro Tyr Pro Glu Phe Leu Glu Leu 275 280 285

Tyr Arg Lys Thr Leu Pro Arg Ser Thr Val Ser Ile Leu Asp Asp His 290 295 300

Ile Ser His Tyr Pro Gln Leu Glu Asp Pro Met Gly Phe Leu Asn Ala 305 310 315 320

Tyr Met Gly Phe Ile Asn Ser Phe 325

<210> 619

<211> 271

<212> PRT

<213> Homo sapiens

<400> 619

Asn Met Asp Pro Pro Gly Leu Gln Gly Val Gln Gly Thr Val Ala Ala 1 5 10 15

Cys Gly Ala Cys Tyr Trp Leu Leu Gly Leu Met Ala Val Arg Ala Ser

Phe Glu Asn Asn Cys Glu Ile Gly Cys Phe Ala Lys Leu Thr Asn Thr 35 40 45

Tyr Cys Leu Val Ala Ile Gly Gly Ser Glu Asn Phe Tyr Ser Val Phe 50 55 60

Glu Gly Glu Leu Ser Asp Thr Ile Pro Val Val His Ala Ser Ile Ala 65 70 75 80

Gly Cys Arg Ile Ile Gly Arg Met Cys Val Gly Asn Arg His Gly Leu 85 90 95

Leu Val Pro Asn Asn Thr Thr Asp Gln Glu Leu Gln His Ile Arg Asn 100 105 110

Ser Leu Pro Asp Thr Val Gln Ile Arg Arg Val Glu Glu Arg Leu Ser 115 120 125

Ala Leu Gly Asn Val Thr Thr Cys Asn Asp Tyr Val Ala Leu Val His
130 135 140

Pro Asp Leu Asp Arg Glu Thr Glu Glu Ile Leu Ala Asp Val Leu Lys
145 150 155 160

Val Glu Val Phe Arg Gln Thr Val Ala Asp Gln Val Leu Val Gly Ser

165 170 175 Tyr Cys Val Phe Ser Asn Gln Gly Gly Leu Val His Pro Lys Thr Ser 185 180 Ile Glu Asp Gln Asp Glu Leu Ser Ser Leu Leu Gln Val Pro Leu Val 200 Ala Gly Thr Val Asn Arg Gly Ser Glu Val Ile Ala Ala Gly Met Val 215 Val Asn Asp Trp Cys Ala Phe Cys Gly Leu Asp Thr Thr Ser Thr Glu Leu Ser Val Val Glu Ser Val Phe Lys Leu Asn Glu Ala Gln Pro Ser 250 Thr Ile Ala Thr Ser Met Arg Asp Ser Leu Ile Asp Ser Leu Thr 265 <210> 620 <211> 88 <212> PRT <213> Homo sapiens

Thr Trp Leu Trp Val Ala Asn Asp Glu Asn Cys Gly Ile Cys Arg Met
20 25 30

Ala Phe Asn Gly Cys Cys Pro Asp Cys Lys Val Pro Gly Asp Asp Cys
35 40 45

Pro Leu Val Trp Gly Gln Cys Ser His Cys Phe His Met His Cys Ile 50 55 60

Leu Lys Trp Leu His Ala Gln Gln Val Gln Gln His Cys Pro Met Cys
65 70 75 80

Arg Gln Glu Trp Lys Phe Lys Glu 85

<210> 621 <211> 46

<212> PRT

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<213> Homo sapiens
<220>
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<222> (35)
<223> Xaa equals any of the naturally occurring L-amino acids (
<220>
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<400> 621
Ala Gly Thr Ser Arg Ser Glu Gly Lys Arg Ser Ser Val Leu Thr Arg
                                     10
Thr Glu Phe Gln Ile Glu Met Phe Gln Thr Ile Glu Gly Glu Lys Trp
Pro Gly Xaa Ser Ile Asn Leu Ser Xaa Phe His Gly Cys Phe
                             40
<210> 622
<211> 103
<212> PRT
<213> Homo sapiens
<220>
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<222> (35)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
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Gly Arg Pro Thr Arg Pro Arg Gly Arg Gly Arg Ser Ser Ala Cys Leu
                                     10
Leu Leu Glu Gly Asp Gly Pro Ala Arg Leu Trp Ala Pro Thr Ser Pro
                                 25
Gly Val Xaa Xaa Glu Arg Phe Ala Glu Glu Arg Gly Ser Gly Arg Ala
         35
                             40
Leu Asn Ala Gly Pro Lys His Pro Gly Ser Leu His Ser Pro Arg Pro
                         55
     50
```

582

Gln Thr Leu Thr Lys Thr Trp Ile Cys Ser Arg Phe Ser Cys Ser Arg

Ser Ser Arg Ser Cys Pro Arg Leu Leu Arg Leu Arg Ala Glu Lys Lys 90 85

Val Cys Gln Ala Trp Thr Gln 100

<210> 623

<211> 103

<212> PRT

<213> Homo sapiens

<220>

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<222> (60)

<223> Xaa equals any of the naturally occurring-L-amino acids

<400> 623

Gly Arg Pro Thr Arg Pro Thr Ser Ser Arg Ser Arg Ala Ala Arg Pro 10

Phe Phe Phe Phe Phe Phe Trp Phe Pro Glu Phe Gly Phe Ile Leu 20

Gln Tyr Arg Asn His Leu Glu Pro Ser Glu Thr Asp Ile Pro Glu Ala 40

Glu Ala Leu Ser Asn Gln Tyr Cys Val Ala Leu Xaa Pro Leu Arg Lys 55

Pro His Leu Gly Tyr Lys Arg Ser Phe Tyr Val Tyr Pro Leu Tyr His 65 70 75

Gly Phe Leu Ser Pro Leu Leu Pro Ile Leu Pro Gly Glu Asn Thr 90

Ala Gln Arg Leu Pro Ser Glu 100

<210> 624

<211> 305

<212> PRT

<213> Homo sapiens

583

<220> <221> SITE <222> (116) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (117) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (219) <223> Xaa equals any of the naturally occurring L-amino acids Thr Gln Asp Leu Trp Met Ser Cys Pro Val Gln Thr Met Asp Pro Glu Val Thr Leu Leu Gln Cys Pro Gly Gly Gly Leu Pro Gln Glu Gln 25 Ile Gln Ala Glu Leu Ser Pro Ala His Asp Arg Arg Pro Leu Pro Gly 35 40 Gly Asp Glu Ala Ile Thr Ala Ile Trp Glu Thr Arg Leu Lys Ala Gln 55 Pro Trp Leu Phe Asp Ala Pro Lys Phe Arg Leu His Ser Ala Thr Leu 70 75 Ala Pro Ile Gly Ser Arg Gly Pro Gln Leu Leu Leu Arg Leu Gly Leu 90 Thr Ser Tyr Arg Asp Phe Leu Gly Thr Asn Trp Ser Ser Ser Ala Ala 105 Trp Leu Arg Xaa Xaa Gly Ala Thr Asp Trp Gly Asp Thr Gln Ala Tyr 115 120 Leu Ala Asp Pro Leu Gly Val Gly Ala Ala Leu Ala Thr Ala Asp Asp 135 Phe Leu Val Phe Leu Arg Arg Ser Arg Gln Val Ala Glu Ala Pro Gly 150 155 Leu Val Asp Val Pro Gly Gly His Pro Glu Pro Gln Ala Leu Cys Pro 165 175 170 Gly Gly Ser Pro Gln His Gln Asp Leu Ala Gly Gln Leu Val Val His 180 185 190

584

Glu Leu Phe Ser Ser Val Leu Gln Glu Ile Cys Asp Glu Val Asn Leu 200 Pro Leu Leu Thr Leu Ser Gln Pro Leu Leu Xaa Gly Ile Ala Arg Asn 210 215 Glu Thr Ser Ala Gly Arg Ala Ser Ala Glu Phe Tyr Val Gln Cys Ser 230 235 Leu Thr Ser Glu Gln Val Arg Lys His Tyr Leu Ser Gly Gly Pro Glu Ala His Glu Ser Thr Gly Ile Phe Phe Val Glu Thr Gln Asn Val Arg Arg Leu Pro Glu Thr Glu Met Trp Ala Glu Leu Cys Pro Ser Pro Lys 280 Ala Pro Ser Ser Ser Thr Thr Gly Phe Arg Glu Val Pro Leu Glu Arg 295 300 Pro 305 <210> 625 <211> 102 <212> PRT <213> Homo sapiens Ser Ala Met Lys Ala Ser Gly Thr Leu Arg Glu Tyr Lys Val Val Gly Arg Cys Leu Pro Thr Pro Lys Cys Arg Thr Pro Pro Leu Tyr Arg Met 25 Arg Ile Phe Ala Pro Asn His Val Val Ala Lys Ser Arg Phe Trp Tyr 40 Phe Val Ser Gln Leu Lys Lys Met Lys Lys Ser Ser Gly Glu Ile Val Tyr Cys Gly Gln Val Phe Glu Lys Ser Pro Leu Arg Val Lys Asn Phe 70 75

Gly Ile Trp Leu Arg Tyr Asp Ser Arg Ser Gly Thr His Asn Met Tyr

85

PCT/US00/05881 WO 00/55173

585

Arg Gly Val Pro Gly Thr 100

<210> 626

<211>`59

<212> PRT

<213> Homo sapiens

<220>

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<222> (36)

<223> Xaa equals any of the naturally occurring L-amino acids

Ala Leu Trp Val Lys Ala Trp Arg Gln Glu Ser Glu Gly Gln Phe Gln

Glu Thr Gln Phe Ile Asn Phe His Gln His Leu Pro Gly Pro Cys Leu 25

Gly Thr Glu Xaa Pro Ser Pro Glu Ser Gly His His Phe Pro Phe Gln 40

Ser Ile Glu Cys Arg Gly Ile Gln Gly Met Gly

<210> 627

<211> 220

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (93)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 627

Arg Leu Val Val Thr Glu Glu Asp Gly Gly Ala Arg Pro Glu Ala Leu 5 10

Gly Lys Ile Ala Pro Arg Thr Pro Ala Glu Leu Gly Ala Arg Ala Asp 20 25

Gln Glu Leu Val Thr Ala Leu Met Cys Asp Leu Arg Arg Pro Ala Ala

Gly Gly Met Met Asp Leu Ala Tyr Val Cys Glu Trp Glu Lys Trp Ser

50 55 60 Lys Ser Thr His Cys Pro Ser Val Pro Leu Ala Cys Ala Trp Ser Cys 70 Arg Asn Leu Ile Ala Phe Thr Met Asp Leu Arg Thr Xaa Asp Gln Asp Leu Thr Arg Met Ile His Ile Leu Asp Thr Glu His Pro Trp Asp Leu His Ser Ile Pro Ser Glu His His Glu Ala Ile Thr Cys Leu Glu Trp 115 Asp Gln Ser Gly Ser Arg Leu Leu Ser Ala Asp Ala Asp Gly Gln Ile Lys Cys Trp Ser Met Ala Asp His Leu Ala Asn Ser Trp Glu Ser Ser 150 155 Val Gly Ser Leu Val Glu Gly Asp Pro Ile Val Ala Leu Ser Trp Leu 165 His Asn Gly Val Lys Leu Ala Leu His Val Glu Lys Ser Gly Ala Ser 185 Ser Phe Gly Glu Lys Phe Ser Arg Val Lys Phe Ser Pro Val Leu Thr Leu Phe Gly Gly Lys Pro Trp Arg Ala Gly Ser Arg 215 <210> 628 <211> 119 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (115) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (117) <223> Xaa equals any of the naturally occurring L-amino acids

Pro Ala Ser Val Glu Val Tyr His Asp Ser Leu Cys Arg Lys Ile Trp

<400> 628

587

1 10 Arg Glu Asp Asp Lys Trp His Val Ile Phe Arg Ala Asp Gly Trp Glu 20 25 Gln His Ile Thr Ala Arg Tyr Leu Val Gly Ala Asp Gly Ala Asn Ser Met Val Arg Arg His Leu Tyr Pro Asp His Gln Ile Arg Lys Tyr Val 55 Ala Ile Gln Gln Trp Phe Ala Glu Lys His Pro Val Pro Phe Tyr Ser Cys Ile Phe Asp Asn Ser Ile Thr Asn Cys Tyr Ser Trp Ser Ile Ser 90 Lys Asp Gly Tyr Phe Ile Phe Gly Gly Ala Tyr Pro Met Glu Arg Arg Ser Asp Xaa Phe Xaa Asp Ala 115 <210> 629 <211> 39 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (30) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (31) <223> Xaa equals any of the naturally occurring L-amino acids

Phe Gly Glu Pro Ser Leu Thr Val Arg Ala Asp Ile Thr Gly Arg Tyr $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$

Ser Ile Val Ser Met Leu Thr Thr Cys Arg Tyr Ser Leu Xaa Xaa His 20 25 30

Met Lys Lys Val Ser Ser Cys

<400> 629

<21	0> 6 1> 2 2> P	67													
<21	3> н	omo :	sapi	ens											
	0> 6: Ala		Leu	Pro 5	Gln	Pro	Thr	Pro	Pro 10	Leu	Thr	Leu	Pro	Gln 15	Ser
Met	Val	Asn	Thr 20	Lys	Pro	Glu	Lys	Thr 25	Glu	Glu	Asp	Ser	Glu 30	Glu	Val
Arg	Glu	Gln 35	Lys	His	Lys	Thr	Phe 40	Val	Glu	Lys	Tyr	Glu 45	Lys	Gln	Ile
Lys	His 50	Phe	Gly	Met	Leu	Arg 55	Arg	Trp	Asp	Asp	Ser 60	Gln	Lys	Tyr	Leu
Ser 65	Asp	Asn	Val	His	Leu 70	Val	Cys	Glu	Glu	Thr 75	Ala	Asn	Tyr	Leu	Val 80
Ile	Trp	Суѕ	Ile	Asp 85	Leu	Glu	Val	Glu	Glu 90	Lys	Cys	Ala	Leu	Met 95	Glu
Gln	Val	Ala	His 100	Gln	Thr	Ile	Val	Met 105	Gln	Phe	Ile	Leu	Glu 110	Leu	Ala
Lys	Ser	Leu 115	Lys	Val	Asp	Pro	Arg 120	Ala	Суѕ	Phe	Arg	Gln 125	Phe	Phe	Thr
Lys	Ile 130	Lys	Thr	Ala	Asp	Arg 135	Gln	Tyr	Met	Glu	Gly 140	Phe	Asn	Asp	Glu
Leu 145	Glu	Ala	Phe	Lys	Glu 150	Arg	Val	Arg	Gly	Arg 155	Ala	Lys	Leu	Arg	11e 160
Glu	Lys	Ala	Met	Lys 165	Glu	Туг	Glu	Glu	Glu 170	Glu	Arg	Lys	Lys	Arg 175	Leu
Gly	Pro	Gly	Gly 180	Leu	Asp	Pro	Val	Glu 185	V al	Tyr	Glu	Ser	Leu 190	Pro	Glu
Glu	Leu	Gln 195	Lys	Cys	Phe	Asp	Val 200	Lys	Asp	Val	Gln	Met 205	Leu	Gln	Asp
Ala	Ile 210	Ser	Lys	Met	Asp	Pro 215	Thr	Asp	Ala	Lys	Tyr 220	His	Met	Gln	Arg
Cys 225	Ile	Asp	Ser	Gly	Leu 230	Trp	Val	Pro	Asn	Ser 235	Lys	Ala	Ser	Glu	Ala 240

589

Lys Glu Gly Glu Glu Ala Gly Pro Gly Asp Pro Leu Leu Glu Ala Val 245 250 255

Pro Lys Thr Gly Asp Glu Lys Asp Val Ser Val 260 265

<210> 631

<211> 207

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (164)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 631

Pro Thr Gly Thr Gly Ser Gly Val Pro Gly Leu Gly Arg Asn Gly Gly
1 5 10 15

Arg Glu Gly Ala Pro Gly Thr Met Gly Leu Leu Thr Ile Leu Lys Lys 20 25 30

Met Lys Glu Lys Glu Arg Glu Leu Arg Leu Leu Met Leu Gly Leu Asp 35 40 45

Asn Ala Gly Lys Thr Thr Ile Leu Lys Lys Phe Asn Gly Glu Asp Ile
50 55 60

Asp Thr Ile Ser Pro Thr Leu Gly Phe Asn Ile Lys Thr Leu Glu His 65 70 75 80

Arg Gly Phe Lys Leu Asn Ile Trp Asp Val Gly Gln Lys Ser Leu 85 90 95

Arg Ser Tyr Trp Arg Asn Tyr Phe Glu Ser Thr Asp Gly Leu Ile Trp
100 105 110

Val Val Asp Ser Ala Asp Arg Gln Arg Met Gln Asp Cys Gln Arg Glu 115 120 125

Leu Gln Ser Leu Leu Val Glu Glu Arg Leu Ala Gly Ala Thr Leu Leu 130 135 140

Ile Phe Ala Asn Lys Gln Asp Leu Pro Gly Ala Leu Ser Ser Asn Ala 145 150 155 160

Ile Arg Glu Xaa Leu Glu Leu Asp Ser Ile Arg Ser His His Trp Cys

590

165 170 175 Ile Gln Gly Cys Ser Ala Val Thr Gly Glu Asn Leu Leu Pro Gly Ile 180 185 Asp Trp Leu Leu Asp Asp Ile Ser Ser Arg Ile Phe Thr Ala Asp 200 <210> 632 <211> 79 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (54) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (60) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (61) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (73) <223> Xaa equals any of the naturally occurring L-amino acids <400> 632 Lys Asn Asn Lys Lys Asp Gln Gln Asn Gly Ile Cys Ser His Thr Met Ile Lys Thr Tyr Leu Arg Thr Ala Leu Phe Met Gly Lys Arg Ser Leu 20 25 30 Ile Asp Ser Gln Phe His Arg Leu Tyr Arg Arg His Gly Leu Gly Arg 35 Pro Gln Gly Asn Leu Xaa Ser Met Val Glu Gly Xaa Xaa Gly Ser Met His His Leu His Trp Pro Glu Gln Xaa Glu Arg Glu Gln Ile Trp

<210> 633 <211> 293 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (249) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (282) <223> Xaa equals any of the naturally occurring L-amino acids <400> 633 Trp Ser Pro Ser Pro Pro Ala Thr Pro Glu Gln Gly Leu Ser Ala Phe Tyr Leu Ser Tyr Phe Asp Met Leu Tyr Pro Glu Asp Ser Ser Trp Ala Ala Lys Ala Pro Gly Ala Ser Ser Arg Glu Glu Pro Pro Glu Glu Pro 35 Glu Gln Cys Pro Val Ile Asp Ser Gln Ala Pro Ala Gly Ser Leu Asp Leu Val Pro Gly Gly Leu Thr Leu Glu Glu His Ser Leu Glu Gln Val Gln Ser Met Val Val Gly Glu Val Leu Lys Asp Ile Glu Thr Ala Cys 85 Lys Leu Leu Asn Ile Thr Ala Asp Pro Met Asp Trp Ser Pro Ser Asn Val Gln Lys Trp Leu Leu Trp Thr Glu His Gln Tyr Arg Leu Pro Pro 120 Met Gly Lys Ala Phe Gln Glu Leu Ala Gly Lys Glu Leu Cys Ala Met 135 130 Ser Glu Glu Gln Phe Arg Gln Arg Ser Pro Leu Gly Gly Asp Val Leu 155 His Ala His Leu Asp Ile Trp Lys Ser Ala Ala Trp Met Lys Glu Arg

592

Thr Ser Pro Gly Ala Ile His Tyr Cys Ala Ser Thr Ser Glu Glu Ser 180 185 190

Trp Thr Asp Ser Glu Val Asp Ser Ser Cys Ser Gly Gln Pro Ile His
195 200 205

Leu Trp Gln Phe Leu Lys Glu Leu Leu Leu Lys Pro His Ser Tyr Gly
210 215 220

Arg Phe Ile Arg Trp Leu Asn Lys Glu Lys Gly Ile Phe Lys Ile Glu 225 230 235 240

Asp Ser Ala Gln Val Ala Arg Leu Xaa Gly Ile Arg Lys Asn Arg Pro 245 250 255

Ala Met Asn Tyr Asp Lys Leu Ser Arg Ser Ile Arg Gln Tyr Tyr Lys 260 265 270

Lys Gly Ile Ile Arg Lys Pro Asp Ile Xaa Gln Arg Leu Val Tyr Gln 275 280 285

Phe Val His Pro Ile 290

<210> 634

<211> 227

<212> PRT

<213> Homo sapiens

<400> 634

Pro Ala Gly Thr Gly Pro Glu Phe Pro Gly Arg Pro Thr Arg Pro Ala
1 5 10 15

Glu Glu Glu Glu Pro Gln Gln Arg Gly Gln Gly Glu Lys Ser Ala 35 40 45

Thr Pro Ser Arg Lys Ile Leu Asp Pro Asn Thr Gly Glu Pro Ala Pro 50 55 60

Val Leu Ser Ser Pro Pro Pro Ala Asp Val Ser Thr Phe Leu Ala Phe 65 70 75 80

Pro Ser Pro Glu Lys Leu Leu Arg Leu Gly Pro Lys Ser Ser Val Leu 85 90 95

Ile Ala Gln Gln Thr Asp Thr Ser Asp Pro Glu Lys Val Val Ser Ala

WO 00/55173

110 100 105 Phe Leu Lys Val Ser Ser Val Phe Lys Asp Glu Ala Thr Val Arg Met 120 Ala Val Gln Asp Ala Val Asp Ala Leu Met Gln Lys Ala Phe Asn Ser 135 Ser Ser Phe Asn Ser Asn Thr Phe Leu Thr Arg Leu Leu Val His Met 150 155 Gly Leu Leu Lys Ser Glu Asp Lys Val Lys Ala Ile Ala Asn Leu Tyr 170 165 Gly Pro Leu Met Ala Leu Asn His Met Val Gln Gln Asp Tyr Phe Pro 185 Lys Ala Leu Ala Pro Leu Leu Leu Ala Phe Val Thr Lys Pro Asn Ser 200 Ala Leu Glu Ser Cys Ser Phe Ala Arg His Ser Leu Leu Gln Thr Leu 220 215 Tyr Lys Val 225 <210> 635 <211> 126 <212> PRT <213> Homo sapiens <400> 635 Thr Ser Gly Cys Ile Ser Asn Gly Lys Met Ser Ser Asn Val Pro Ala Asp Met Ile Asn Leu Arg Leu Ile Leu Val Ser Gly Lys Thr Lys Glu 25 Phe Leu Phe Ser Pro Asn Asp Ser Ala Ser Asp Ile Ala Lys His Val Tyr Asp Asn Trp Pro Met Asp Trp Glu Glu Glu Gln Val Ser Ser Pro Asn Ile Leu Arg Leu Ile Tyr Gln Gly Arg Phe Leu His Gly Asn Val Thr Leu Gly Ala Leu Lys Leu Pro Phe Gly Lys Thr Thr Val Met His 90

594

Leu Val Ala Arg Glu Thr Leu Pro Glu Pro Asn Ser Gln Gly Gln Arg
100 105 110

Asn Arg Glu Lys Thr Gly Glu Ser Asn Cys Cys Val Ile Leu 115 120 125

<210> 636

<211> 195

<212> PRT

<213> Homo sapiens

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<222> (96)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 636

Val Ser Gly Phe Ala Gly Pro Ala Ser Leu Ile Ser Met Lys Leu Leu 1 5 10 15

Ser Leu Val Ala Val Val Gly Cys Leu Leu Val Pro Pro Ala Glu Ala 20 25 30

Asn Lys Ser Ser Glu Asp Ile Arg Cys Lys Cys Ile Cys Pro Pro Tyr 35 40 45

Arg Asn Ile Ser Gly His Ile Tyr Asn Gln Asn Val Ser Gln Lys Asp
50 60

Cys Asn Cys Leu His Val Val Glu Pro Met Pro Val Pro Gly His Asp
65 70 75 80

Val Glu Ala Tyr Cys Leu Leu Cys Glu Cys Arg Tyr Glu Glu Arg Xaa 85 90 95

Thr Thr Thr Ile Lys Val Ile Ile Val Ile Tyr Leu Ser Val Val Gly
100 105 110

Ala Leu Leu Tyr Met Ala Phe Leu Met Leu Val Asp Pro Leu Ile 115 120 125

Arg Lys Pro Asp Ala Tyr Thr Glu Gln Leu His Asn Glu Glu Glu Asn 130 135 140

Glu Asp Ala Arg Ser Met Ala Ala Ala Ala Ala Ser Leu Gly Gly Pro 145 150 155 160

Arg Ala Asn Thr Val Leu Glu Arg Val Glu Gly Ala Gln Gln Arg Trp

595

175 165 170 Lys Leu Gln Val Gln Glu Gln Arg Lys Thr Val Phe Asp Arg His Lys 185 190 Met Leu Ser 195 <210> 637 <211> 159 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (92) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (115) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (138) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (151) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (156) <223> Xaa equals any of the naturally occurring L-amino acids <400> 637 Arg Pro Thr Arg Pro Gly Asn Ser Arg Arg Arg Gly Arg Arg Gly Cys 10 Trp Arg Leu Leu Gly Phe Gly Ala Ala Ala Ile Met Pro Gly Ile Val 20 25 30 Glu Leu Pro Thr Leu Glu Asp Leu Lys Val Gln Glu Val Lys Val Ser 35

Ser Ser Val Leu Lys Ala Ala Ala His His Tyr Gly Val Gln Cys Asp

596

50 55 60

Lys Pro Asn Lys Glu Phe Met Leu Cys Arg Trp Glu Glu Lys Asp Pro 65 70 75 80

Arg Arg Cys Leu Glu Glu Gly Lys Leu Val Asn Xaa Cys Ala Leu Asp 85 90 95

Phe Phe Arg Gln Ile Lys Leu Ser Leu Cys Arg Ala Phe Tyr Arg Leu 100 105 110

Leu Asp Xaa His Arg Leu Leu Arg Pro Ala Val Phe Ser Ser Leu Pro
115 120 125

Gln Thr Ala Gly Gln Phe Asp Asp Val Xaa Gly Ala Thr Gly Met Val 130 135 140

Arg Leu Asn Trp Gly Lys Xaa Ser Ser His Gln Xaa Glu Asn Ser 145 150 155

<210> 638

<211> 20

<212> PRT

<213> Homo sapiens

<400> 638

Phe Ser Arg Asp Lys Val Ser Pro Cys Trp Pro Gly Trp Ser Arg Thr 1 5 10 15

Pro Gly Leu Arg

20

<210> 639

<211> 408

<212> PRT

<213> Homo sapiens

<400> 639

Thr Trp Gly Gln Thr Pro Cys Ser Pro Gly His Gly Gln Arg Pro Ser 1 5 10 15

Ser Thr Cys Leu Thr Val Gly Pro Gly Gly Pro Ser Leu Gly Arg

Pro Cys Pro Gln Leu Leu Gln Phe Gly Val Leu Phe Cys Thr Ile 35 40 45

rea	50		reu	тгр	val	55		Pne	Leu	туг	60		Pne	туг	туг
Ser 65		Met	Pro	Thr	Val 70	Ser	His	Leu	Ser	Pro 75	Val	His	Phe	Tyr	Tyr 80
Arg	Thr	Asp	Cys	Asp 85	Ser	Ser	Thr	Thr	Ser 90	Leu	Cys	Ser	Phe	Pro 95	Val
Ala	Asn	Val	Ser 100	Leu	Thr	Lys	Gly	Gly 105	Arg	Asp	Arg	Val	Leu 110	Met	Tyr
Gly	Gln	Pro 115	Tyr	Arg	Val	Thr	Leu 120	Glu	Leu	Glu	Leu	Pro 125	Glu	Ser	Pro
Val	Asn 130	Gln	Asp	Leu	Gly	Met 135	Phe	Leu	Val	Thr	Ile 140	Ser	Cys	Tyr	Thr
Arg 145	Gly	Gly	Arg	Ile	11e 150	Ser	Thr	Ser	Ser	Arg 155	Ser	Val	Met	Leu	His 160
Tyr	Arg	Ser	Asp	Leu 165	Leu	Gln	Met	Leu	Asp 170	Thr	Leu	Val	Phe	Ser 175	Ser
Leu	Leu	Leu	Phe 180	Gly	Phe	Ala	Glu	Gln 185	Lys	Ġln	Leu	Leu	Glu 190	Val	Glu
Leu	Tyr	Ala 195	Asp	Tyr	Arg	Glu	Asn 200	Ser	Tyr	Val	Pro	Thr 205	Thr	Gly	Ala
Ile	Ile 210	Glu	Ile	His	Ser	Lys 215	Arg	Ile	Gln	Leu	Tyr 220	Gly	Ala	Tyr	Leu
Arg 225	Ile	His	Ala	His	Phe 230	Thr	Gly	Leu	Arg	Tyr 235	Leu	Leu	Tyr	Asn	Phe 240
Pro	Met	Thr	Cys	Ala 245	Phe	Ile	Gly	Val	Ala 250	Ser	Asn	Phe	Thr	Phe 255	Leu
Ser	Val	Ile	Val 260	Leu	Phe	Ser	Tyr	Met 265	Gln	Trp	Val	Trp	Gly 270	Gly	Ile
rp	Pro	Arg 275	His	Arg	Phe	Ser	Leu 280	Gln	Val	Asn	Ile	Arg 285	Lys	Arg	Asp
	290	Arg				295					300				
Pro 305	Glu	Gly	Gln	Glu	Glu 310	Ser	Thr	Pro	Gln	Ser 315	Asp	Val	Thr	Glu	Asp 320

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Gly Glu Ser Pro Glu Asp Pro Ser Gly Thr Glu Gly Gln Leu Ser Glu
                                                         335
                325
                                    330
Glu Glu Lys Pro Asp Gln Gln Pro Leu Ser Gly Glu Glu Leu Glu
                                345
Pro Glu Ala Ser Asp Gly Ser Gly Ser Trp Glu Asp Ala Ala Leu Leu
                            360
Thr Glu Ala Asn Leu Pro Ala Pro Ala Pro Ala Ser Ala Ser Ala Pro
                       375
                                            380
    370
Val Leu Glu Thr Leu Gly Ser Ser Glu Pro Ala Gly Gly Ala Leu Arg
385
                    390
                                        395
Gln Arg Pro Thr Cys Ser Ser Ser
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<22	0>														
<22	1> S	ITE													
<22	2> (:	276)													
	•	•	qual	s an	y of	the	nat	ural	ly o	ccur	ring	L-a	mino	acio	ds
<220	0>														
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<222	2> (2	286)													
<223	3> X	aa e	qual	s an	y of	the	nati	ural	ly o	ccur	ring	L-a	mino	acio	ds
)> 64														
Phe 1	Ser	Ser	Ser	Ala 5	Cys	Pro	Ser	Val	Xaa 10	Ser	Leu	Phe	Val	Xaa 15	Leu
01	•		5	•• : -	• • •	• • •	01 -	a1	•• -	D	3		C	61	2
GIÀ	ьys	ASII	20	HIS	Asp	MIG	GIN	25	nis	Pro	Arg	ALG	30	GIU	Asp
	_	_	_		_				_	_	_	-1	~1		~ 1
GIN	Pro	Ser 35	ser	GLY	rys	Pro	Va1	Thr	Ser	Tyr	Pro	45	GIU	cys	СТА
Phe	Val 50	Phe	Thr	Lys	Glu	Ala 55	Ser	Leu	Glu	Ile	Arg 60	Asp	Met	Leu	Leu
	50					,,,					00				
Ala	Asn	Lys	Val	Pro	Ala	Ala	Ala	Arg	Ala	Gly	Ala	Ile	Ala	Pro	
65					70					75					80
Glu	Val	Thr	Val	Pro	Ala	Gln	Asn	Thr	Gly	Leu	Gly	Pro	Glu	Lys	Thr
				85					90					95	
Ser	Phe	Phe	Gln	Ala	T.e.u	Glv	Tle	ጥክ r	Thr	Lys	Tle	Ser	Ara	Glv	Thr
DEI	riic	F 11C	100	niu	DCu	Cly	110	105	11	Lys	110	JCI	110	01	
													_	_	
Ile	Glu		Leu	Ser	Asp	Val		Leu	Ile	Lys	Thr	G1y 125	Asp	Lys	Val
		115					120					123			
Gly	Ala	Ser	Glu	Ala	Thr	Leu	Leu	Asn	Met	Leu	Asn	Ile	Ser	Pro	Phe
	130					135					140				
Ser	Phe	Glv	Leu	Ile	Ile	Gln	Gln	Val	Phe	Asp	Asn	Glv	Ser	Ile	Tyr
145	=	-4			150					155		3			160
N	Dwa	C1	17. 1	T 0	7.6=	T1-	mh	C1	~1	m	T	u: ~	Co-	7	Dh.
нSП	PEO	GIU	vdI	165	ASP	TTE	THE	GIU	170	Thr	ren	ura	ser	175	rne
									1,0					-,,	
Leu	Glu	Gly		Arg	Asn	Val	Ala		Val	Cys	Leu	Gln		Gly	Tyr
			180					105					190		

Pro Thr Val Ala Ser Val Pro His Ser Ile Ile Asn Gly Tyr Lys Arg 195 200 205

Val Leu Ala Leu Ser Val Glu Thr Asp Tyr Thr Phe Pro Leu Ala Glu 215

Lys Val Lys Ala Phe Leu Ala Asp Pro Ser Ala Phe Val Ala Ala Ala 235 230

Pro Val Ala Ala Ala Thr Thr Ala Ala Pro Ala Ala Ala Ala Pro 245 250

Ala Lys Val Glu Ala Lys Glu Glu Ser Glu Glu Xaa Asp Glu Xaa Ile 265

Xaa Xaa Ser Xaa Ile Ser Lys Ser Asn Asn Ser Ser Gln Xaa Ile Val 280

<210> 641

<211> 444

<212> PRT

<213> Homo sapiens

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<223> Xaa equals any of the naturally occurring L-amino acids

<400> 641

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Ser Asp Lys Asp Ile Phe Gly Asp Ala Cys Asp Asn Cys Leu Ser Val 20 25

Leu Xaa Asn Asp Gln Lys Asp Thr Asp Gly Asp Gly Arg Gly Asp Ala

Cys Asp Asp Met Asp Gly Asp Gly Ile Lys Asn Ile Leu Asp Asn 55

Cys Pro Lys Phe Pro Asn Arg Asp Gln Arg Asp Lys Asp Gly Asp Gly 65 70

Val Gly Asp Ala Cys Asp Ser Cys Pro Asp Val Ser Asn Pro Asn Gln 85 90

ser	Asp	vai	100	ASN	ASP	ren	vai	105	Asp	Ser	cys	Азр	110	ASII	GIN
Asp	Ser	Asp 115	Gly	Asp	Gly	His	Gln 120	Asp	Ser	Thr	Asp	Asn 125	Cys	Pro	Thr
Val	Ile 130	Asn	Ser	Ala	Gln	Leu 135	Asp	Thr	Asp	Lys	Asp 140	Gly	Ile	Gly	Asp
Glu 145	Cys	Asp	Asp	Asp	Asp 150	Asp	Asn	Asp	Gly	Ile 155	Pro	Asp	Leu	Val	Pro 160
Pro	Gly	Pro	Asp	Asn 165	Cys	Arg	Leu	Val	Pro 170	Asn	Pro	Ala	Gln	Glu 175	Asp
Ser	Asn	Ser	Asp 180	Gly	Val	Gly	Asp	Ile 185	Cys	Glu	Ser	Asp	Phe 190	Asp	Gln
Asp	Gln	Val 195	Ile	Asp	Arg	Ile	Asp 200	Val	Cys	Pro	Glu	Asn 205	Ala	Glu	Val
Thr	Leu 210	Thr	Asp	Phe	Arg	Ala 215	Tyr	Gln	Thr	Val	Val 220	Leu	Asp	Pro	Glu
Gly 225	Asp	Ala	Gln	Ile	Asp 230	Pro	Asn	Trp	Val	Val 235	Leu	Asn	Gln	Gly	Met 240
Glu	Ile	Val	Gln	Thr 245	Met	Asn	Ser	Asp	Pro 250	Gly	Leu	Ala	Val	Gly 255	Tyr
Thr	Ala	Phe	Asn 260	Gly	Val	Asp	Phe	G1u 265	Gly	Thr	Phe	His	Val 270	Asn	Thr
Gln	Thr	Asp 275	Asp	Asp	Tyr	Ala	Gly 280	Phe	Ile	Phe	Gly	Туг 285	Gln	Asp	Ser
Ser	Ser 290	Phe	Tyr	Val	Val	Met 295	Trp	Lys	Gln	Thr	Glu 300	Gln	Thr	Tyr	Trp
31n 305	Ala	Thr	Pro	Phe	Arg 310	Ala	Val	Ala	Glu	Pro 315	Gly	Ile	Gln	Leu	Lys 320
Ala	Val	Lys	Ser	Lys 325	Thr	Gly	Pro	Gly	Glu 330	His	Ĺeu	Arg	Asn	Ser 335	Leu
rp	His	Thr	Gly 340	Asp	Thr	Ser	Asp	Gln 345	Val	Arg	Leu	Leu	Trp 350	Lys	Asp
Ser	Arg	Asn 355	Val	Gly	Trp		Asp 360	-	Val	Ser		Arg 365	Trp	Phe	Leu

Gln His Arg Pro Gln Val Gly Tyr Ile Arg Val Arg Phe Tyr Glu Gly 375 Ser Glu Leu Val Ala Asp Ser Gly Val Thr Ile Asp Thr Thr Met Arg 395 Gly Gly Arg Leu Gly Val Phe Cys Phe Ser Gln Glu Asn Ile Ile Trp 405 Ser Asn Leu Lys Tyr Arg Cys Asn Asp Thr Ile Pro Glu Asp Phe Gln Glu Phe Gln Thr Gln Asn Phe Asp Arg Phe Asp Asn 440 <210> 642 <211> 326 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (50) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (296) <223> Xaa equals any of the naturally occurring L-amino acids <400> 642 Ser Ala Arg Ala Ser Asp Leu Gly Ala Pro Arg Thr Trp Thr Gly Ala Ala Ala Gly Pro Arg Thr Pro Ser Ala His Ile Pro Val Pro Ala Gln 20 25 30 Arg Ala Thr Pro Gly Lys Ala Arg Leu Asp Glu Val Met Ala Ala Ala Ala Xaa Thr Ser Leu Ser Thr Ser Pro Leu Leu Gly Ala Pro Val Ala Ala Phe Ser Pro Glu Pro Gly Leu Glu Pro Trp Lys Glu Ala Leu

Val Arg Pro Pro Gly Ser Tyr Ser Ser Ser Ser Asn Ser Gly Asp Trp

90

603

Gl	y Trp	Asp	Leu 100	Ala	Ser	Asp	Gln	Ser 105	Ser	Pro	Ser	Thr	Pro 110	Ser	Pro
Pr	o Leu	Pro 115	Pro	Glu	Ala	Ala	His 120	Phe	Leu	Phe	Gly	Glu 125	Pro	Thr	Leu
Ar	g Lys 130	Arg	Lys	Ser	Pro	Ala 135	Gln	Val	Met	Phe	Gln 140	Cys	Leu	Trp	Lys
5e 14	r Cys 5	Gly	Lys	Val	Leu 150	Ser	Thr	Ala	Ser	Ala 155	Met	Gln	Arg	His	Ile 160
Ar	g Leu	Val	His	Leu 165	Gly	Arg	Gln	Ala	Glu 170	Pro	Asp	Gln	Ser	Asp 175	Gly
Gl	u Glu	Asp	Phe 180	туг	Tyr	Thr	Glu	Leu 185	Asp	Val	Gly	Val	Asp 190	Thr	Leu
Th	r Asp	Gly 195	Leu	Ser	Ser	Leu	Thr 200	Pro	Val	Ser	Pro	Thr 205	Ala	Ser	Met
Pr	210	Ala	Phe	Pro	Arg	Leu 215	Glu	Leu	Pro	Glu	Leu 220	Leu	Glu	Pro	Pro
A1 22	a Leu 5	Pro	Ser	Pro	Leu 230	Arg	Pro	Pro	Ala	Pro 235	Pro	Leu	Pro	Pro	Pro 240
Pr	o Val	Leu	Ser	Thr 245	Val	Ala	Asn	Pro	Gln 250	Ser	Cys	His	Ser	Asp 255	Arg
۷a	l Tyr	Gln	Gly 260	Cys	Leu	Thr	Pro	Ala 265	Arg	Leu	Glu	Pro	Gln 270	Pro	Thr
Gl	u Val	Gly 275	Ala	Cys	Pro	Pro	Ala 280	Leu	Ser	Ser	Arg	Ile 285	Gly	Val	Thr
Le	1 Arg 290	Lys	Pro	Arg	Gly	Asp 295	Xaa	Lys	Lys	Cys	Arg 300	Lys	Val	Tyr	Gly

Met Glu Arg Arg Asp Leu Trp Cys Thr Ala Cys Arg Trp Lys Lys Ala

315

320

Cys Gln Arg Phe Leu Asp 325

310

<210> 643 <211> 129

305

<212> PRT

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<213> Homo sapiens
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                                                          15
                  5
                                     10
 1
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Gln Xaa Xaa Leu Leu Glu Gln Xaa Asp Leu Leu Ala Gly Leu Ile Ser

25 20 Asn Ser Ser Asp Ala Xaa Asp Lys Ile Arg Tyr Glu Ser Leu Thr Asp Pro Ser Lys Leu Asp Ser Gly Lys Glu Leu His Ile Asn Leu Ile Pro 55 Asn Lys Gln Asp Arg Thr Leu Thr Ile Val Gly Tyr Arg Asp Arg Met Thr Lys Ala Asp Leu Ile Asn Asn Leu Gly Thr Ile Ala Xaa Ser Gly Thr Lys Ala Phe Met Glu Xaa Leu Gln Ala Gly Ala Asp Ile Ser Met 105 Ile Gly Gln Phe Gly Val Gly Phe Tyr Ser Ala Tyr Leu Val Ala Arg 115 120 Arg <210> 644 <211> 156 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (12) <223> Xaa equals any of the naturally occurring L-amino acids <400> 644 Ser Thr His Ala Ser Ala Ser Arg Arg Leu Leu Xaa Asp Val Cys Gln Asp Cys Ile Gln Met Val Thr Asp Ile Gln Thr Ala Val Arg Thr Asn 20 25 Ser Thr Phe Val Glu Ala Leu Val Asp His Ala Lys Ala Gln Cys Asp Leu Leu Gly Pro Gly Met Ala Asp Met Cys Lys Asn Tyr Ile Asn Gln 55

Tyr Ser Asp Ile Ala Val Gln Met Met His Met Gln Pro Lys Glu

Ile Cys Gly Leu Val Gly Phe Cys Asp Gln Val Lys Glu Met Pro Met
85 90 95

Gln Thr Leu Ile Pro Ala Lys Ala Val Ser Glu Asn Val Ile Pro Ala 100 - 105 110

Leu Glu Leu Val Glu Pro Ile Lys Lys Asp Thr Val Gln Ala Lys Thr 115 120 125

Ser Val Ser Cys Gly Asp Met Arg Val Thr Trp Leu Lys Glu Val Ala 130 135 140

Lys Leu His Trp Thr Thr Gly Leu Arg Lys Lys 145 150 155

<210> 645

<211> 115

<212> PRT

<213> Homo sapiens

<400> 645

Ala Asp Pro Gly Val Gly Ala Val Pro Gly Leu Ala Ala Asp Leu Ala 1 5 10 15

Thr Ala Ala Arg Ser Leu Gly Pro Ala Leu Val Leu Asp Leu Gly Arg

Pro Pro Ser Pro Asp Pro His Glu Gly Pro Ser Pro Ser Pro Arg Arg
35 40 45

Ser Pro Asp Leu Val Arg Gly Pro Gly Pro Gly Leu Gly Pro Gly Val 50 60

Leu Pro Gln Cys Pro Arg Gly Asn Pro Asn Pro Gly Arg Asp Arg Arg 65 70 .75 80

Val Pro Pro Ser Leu Leu Lys Arg Lys Glu Arg Cys Pro Leu Lys Lys 85 90 95

Met Val Met Ser Gly Asn Pro Arg His Ile Thr Leu Ile His Lys Trp 100 105 110

Asp Leu Gly

607

<211> 153 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (127) <223> Xaa equals any of the naturally occurring L-amino acids <400> 646 Tyr Met Pro Asn Gly Ser Leu Asn Glu Leu Leu His Arg Lys Thr Glu Tyr Pro Asp Val Ala Trp Pro Leu Arg Phe Arg Ile Leu His Glu Ile 25 Ala Leu Gly Val Asn Tyr Leu His Asn Met Thr Pro Pro Leu Leu His His Asp Leu Lys Thr Gln Asn Ile Leu Leu Asp Asn Glu Phe His Val Lys Ile Ala Asp Phe Gly Leu Ser Lys Trp Arg Met Met Ser Leu Ser 70 75 Gln Ser Arg Ser Ser Lys Ser Ala Pro Glu Gly Gly Thr Ile Ile Tyr Met Pro Pro Glu Asn Tyr Glu Pro Gly Gln Lys Ser Arg Ala Ser Ile 105 Lys His Asp Ile Tyr Ser Tyr Ala Val Ile Thr Trp Glu Val Xaa Ser Arg Lys Gln Pro Phe Glu Asp Val Thr Asn Pro Leu Gln Ile Met Tyr Ser Val Ser Gln Gly His Trp Thr Gly <210> 647 <211> 220 <212> PRT <213> Homo sapiens <400> 647

Ala Ser Glu Gln Gly Ala Val Gly Gln Gly Gly Leu Ala Gly Val Pro

10

608

Thr Leu Thr Ser Leu Pro Ser Ser Cys Pro Glu Pro Arg Pro Ser Met 20 25 30

Asp Ala Val Asp Ala Thr Met Glu Lys Leu Arg Ala Gln Cys Leu Ser 35 40 45

Arg Gly Ala Ser Gly Ile Gln Gly Leu Ala Arg Phe Phe Arg Gln Leu $50 \hspace{1cm} 55 \hspace{1cm} 60 \hspace{1cm}$

Asp Arg Asp Gly Ser Arg Ser Leu Asp Ala Asp Glu Phe Arg Gln Gly 65 70 75 80

Leu Ala Lys Leu Gly Leu Val Leu Asp Gln Ala Glu Ala Glu Gly Val 85 90 95

Cys Arg Lys Trp Asp Arg Asn Gly Ser Gly Thr Leu Asp Leu Glu Glu 100 105 110

Phe Leu Arg Ala Leu Arg Pro Pro Met Ser Gln Ala Arg Glu Ala Val 115 120 125

Ile Ala Ala Ala Phe Ala Lys Leu Asp Arg Ser Gly Asp Gly Val Val
130 135 140

Thr Val Asp Asp Leu Arg Gly Val Tyr Ser Gly Arg Ala His Pro Lys
145 150 155 160

Val Arg Ser Gly Glu Trp Thr Glu Asp Glu Val Leu Arg Arg Phe Leu 165 170 175

Asp Asn Phe Asp Ser Ser Glu Lys Asp Gly Gln Val Thr Leu Ala Glu 180 185 190

Phe Gln Asp Tyr Tyr Ser Gly Val Ser Ala Ser Met Asn Thr Asp Glu 195 200 205

Glu Phe Val Ala Met Met Thr Ser Ala Trp Gln Leu 210 215 220

<210> 648

<211> 118

<212> PRT

<213> Homo sapiens

<400> 648

Asp Asn Arg Thr Leu Thr Lys Gly Pro Asp Thr Val Gly Thr Met Gly
1 5 10 15

Gln Cys Arg Ser Ala Asn Ala Glu Asp Ala Gln Glu Phe Ser Asp Val

609

30

25

20

Glu Arg Ala Ile Glu Thr Leu Ile Lys Asn Phe His Gln Tyr Ser Val 40 Glu Gly Gly Lys Glu Thr Leu Thr Pro Ser Glu Leu Arg Asp Leu Val 50 55 Thr Gln Gln Leu Pro His Leu Met Pro Ser Asn Cys Gly Leu Glu Glu 70 75 Lys Ile Ala Asn Leu Gly Ser Cys Asn Asp Ser Lys Leu Glu Phe Arg 90 85 Ser Phe Trp Glu Leu Ile Gly Glu Ala Ala Lys Ser Val Lys Leu Glu 105 Arg Pro Val Arg Gly His 115 <210> 649 <211> 309 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (77) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (160) <223> Xaa equals any of the naturally occurring L-amino acids Asp His His Gln Gly Ala Glu Ser Val Pro Gly Ile Gly Val Ser Pro 10 Thr Ser Ser Ser Cys Pro Pro Thr Ser Cys Thr Gln Pro Val Thr 25 Thr Trp Ser Pro Gly Leu Arg Val Glu Ser Leu Asp Gly Ala Lys Thr Gly Lys Gly Ala Leu Thr Gly Ala Pro Gly Ser Phe Gly Ser Ser Glu 50 55 Phe Leu Thr Gly Leu Arg Asn Thr Ser Glu Ala Arg Xaa Thr Arg Gly

65					70					75					80
Pro	Ile	Met	Gln	Glu 85	Pro	Arg	Arg	Val	Thr 90	Pro	Cys	Leu	Gly	Lys 95	Arg
Gly	Val	Lys	Thr 100	Pro	Gln	Leu	Gln	Pro 105	Gly	Ser	Ala	Phe	Leu 110	Pro	Arg
Val	Arg	Arg 115	Gln	Ser	Phe	Pro	Ala 120	Arg	Ser	Asp	Ser	Tyr 125	Thr	Thr	Val
Arg	Asp 130	Phe	Leu	Ala	Val	Pro 135	Arg	Thr	Ile	Ser	Ser 140	Ala	Ser	Ala	Thr
Leu 145	Ile	Met	Ala	Val	Ala 150	Val	Ser	His	Phe	Arg 155	Pro	Gly	Pro	Glu	Xaa 160
Trp	Asp	Thr	Ala	Ser 165	Met	Ala	Ala	Ser	Lys 170	Val	Lys	Gln	Asp	Met 175	Pro
Pro	Pro	Gly	Gly 180	Туг	Gly	Pro	Ile	Asp 185	Tyr	Lys	Arg	Asn	Leu 190	Pro	Arg
Arg	Gly	Leu 195	Ser	Gly	Tyr	Ser	Met 200	Leu	Ala	Ile	Gly	11e 205	Gly	Thr	Leu
Ile	Туг 210	Gly	His	Trp	Ser	Ile 215	Met	Lys	Trp	Asn	Arg 220	Glu	Arg	Arg	Arg
Leu 225	Gln	Ile	Glu	Asp	Phe 230	Glu	Ala	Ārg	Ile	Ala 235	Leu	Leu	Pro	Leu	Leu 240
Gln	Ala	Glu	Thr	Asp 245	Arg	Arg	Thr	Leu	Gln 250	Met	Leu	Arg	Glu	Asn 255	Leu
Glu	Glu	Glu	Ala 260	Ile	Ile	Met	Lys	Asp 265	Val	Pro	Asp	Trp	Lys 270	Val	Gly
Glu	Ser	Val 275	Phe	His	Thr	Thr	Arg 280	Trp	Val	Pro	Pro	Leu 285	Ile	Gly	Glu
Leu	Туг 290	Gly	Leu	Arg	Thr	Thr 295	Glu	Glu	Ala	Leu	His 300	Ala	Ser	His	Gly
Phe 305	Met	Trp	Tyr	Thr											

<210> 650 <211> 286

	2> P 3> H	RT omo	sapi	ens											
	0> 6		•	- 1-	m b		5 .	1	• • •			a	, 61 -		-1
1	PIO	Thr	Leu	11e 5	Thr	Ala	Pne	vaı	10	АІА	Thr	ser	GIN	Ala 15	GII
Ala	Gly	Trp	Leu 20	Gln	His	Asp	Tyr	Gly 25	His	Leu	Ser	Val	Tyr 30	Arg	Lys
Pro	Lys	Trp 35	Asn	His	Leu	Val	His 40	Lys	Phe	Val	Ile	Gly 45	His	Leu	Lys
Gly	Ala 50	Ser	Ala	Asn	Trp	Trp 55	Asn	His	Arg	His	Phe 60	Gln	His	His	Ala
Lys 65	Pro	Asn	·Ile	Phe	His 70	Lys	Asp	Pro	Asp	Val 75	Asn	Met	Leu	His	Va] 80
Phe	Val	Leu	Gly	Glu 85	Trp	Gln	Pro	Ile	Glu 90	Tyr	Gly	Lys	Lys	Lys 95	Let
Lys	Tyr	Leu	Pro 100	Tyr	Asn	His	Gln	His 105	Glu	туг	Phe	Phe	Leu 110	Ile	Gly
Pro	Pro	Leu 115	Leu	Ile	Pro	Met	Туг 120	Phe	Gln	Tyr	Gln	Ile 125	Ile	Met	Thr
Met	Ile 130	Val	His	Lys	Asn	Trp 135	Val	Asp	Leu	Ala	Trp 140	Ala	Val	Ser	туг
Tyr 145	Ile	Arg	Phe	Phe	Ile 150	Thr	Tyr	Ile	Pro	Phe 155	туг	Gly	Ile	Leu	Gly 160
Ala	Leu	Leu	Phe	Leu 165	Asn	Phe	Ile	Arg	Phe 170	Leu	Glu	Ser	His	Trp 175	Phe
Val	Trp	Val	Thr 180	Gln	Met	Asn	His	Ile 185	Val	Met	Glu	Ile	Asp 190	Gln	Glu
Ala	Tyr	Arg 195	Asp	Trp	Phe	Ser	Ser 200	Gln	Leu	Thr	Ala	Thr 205	Суз	Asn	Val
Glu	Gln 210	Ser	Phe	Phe	Asn	Asp 215	Trp	Phe	Ser	Gly	His 220	Leu	Asn	Phe	Gln
Ile 225	Glu	His	His	Leu	Phe 230	Pro	Thr	Met	Pro	Arg 235	His	Asn	Leu	His	Lys 240
Ile	Ala	Pro	Leu	Val 245	Lys	Ser	Leu	Cys	Ala 250	Lys	His	Gly	Ile	Glu 255	Tyr

Gln Glu Lys Pro Leu Leu Arg Ala Leu Leu Asp Ile Ile Arg Ser Leu 260 265 270

Lys Lys Ser Gly Lys Leu Trp Leu Asp Ala Tyr Leu His Lys 275 280 285

<210> 651

<211> 184

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<213> Homo sapiens

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<221> SITE

<222> (35)

<223> Xaa equals any of the naturally occurring L-amino acids

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<223> Xaa equals any of the naturally occurring L-amino acids

<400> 651

Glu Arg Gly Pro Ile Pro Val Cys Pro His Lys Ala Ala Ser Ser Val
1 5 10 15

Ile Ser Leu Leu Arg Ala Glu Leu Arg Leu Tyr Thr Asp Pro His Lys 20 25 30

Tyr His Xaa Phe Cys Leu Arg Lys Asp Lys Ala His Val Cys Phe Cys 35 40 45

Phe Arg Phe Leu Phe Ser Phe Phe Xaa Glu Ala Leu Trp Arg Ser Met 50 55 60

Phe Leu Leu Ser Phe Leu Xaa Lys Pro Ser Phe Trp Ala Thr Gly Leu 65 70 75 80

Ile Leu Ser Thr Ser Ser Phe Pro Pro Phe Ser Ile Val Ser Leu Pro

95 90 85 Pro Ser His Pro Thr Arg Ala Pro Leu Xaa Leu Ser Phe Pro Ser Ser 100 105 110 Pro Ala Val Ser Phe Leu Arg Ser Gly Thr Lys Leu Ile Phe Arg Arg 120 Arg Pro Arg Gln Lys Glu Ala Gly Leu Ser Gln Ser His Asp Asp Leu 135 Ser Asn Ala Thr Ala Thr Pro Ser Val Arg Lys Lys Ala Gly Ser Phe 150 155 _, Ser Arg Arg Leu Ile Lys Arg Phe Ser Phe Lys Ser Lys Pro Lys Ala 170 Asn Gly Asn Pro Ser Pro Gln Leu 180 <210> 652 <211> 641 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (438) <223> Xaa equals any of the naturally occurring L-amino acids <400> 652 Gln Gly Ser Glu Pro Ser Ser Glu Asn Ala Asn Asp Thr Ile Ile Leu . 5 Arg Asn Leu Asn Pro His Ser Thr Met Asp Ser Ile Leu Gly Ala Leu Ala Pro Tyr Ala Val Leu Ser Ser Ser Asn Val Arg Val Ile Lys Asp Lys Gln Thr Gln Leu Asn Arg Gly Phe Ala Phe Ile Gln Leu Ser Thr Ile Glu Ala Ala Gln Leu Leu Gln Ile Leu Gln Ala Leu His Pro Pro

Leu Thr Ile Asp Gly Lys Thr Ile Asn Val Glu Phe Ala Lys Gly Ser

85

гуз	ALG	мар	100	AIG	361	ASII	GIU	105	Ser	ALG	116	261	110	AIG	QC1
Val	Ala	Ser 115	Thr	Ala	Ile	Ala	Ala 120	Ala	Gln	Trp	Ala	Ile 125	Ser	Gln	Ala
Ser	Gln 130	Gly	Gly	Glu	Gly	Thr 135	Trp	Ala	Thr	Ser	Glu 140	Glu	Pro	Pro	Val
Asp 145	Tyr	Ser	Tyr	Tyr	Gln 150	Gln	Asp	Glu	Gly	Туг 155	Gly	Asn	Ser	Gln	Gly 160
Thr	Glu	Ser	Ser	Leu 165	Tyr	Ala	His	Gly	Tyr 170	Leu	Lys	Gly	Thr.	Lys 175	Gly
Pro	Gly	Ile	Thr 180	Gly	Thr	Lys	Gly	Asp 185	Pro	Thr	Gly	Ala	Gly 190	Pro	Glu
Ala	Ser	Leu 195	Glu	Pro	Gly	Ala	Asp 200	Ser	Val	Ser	Met	Gln 205	Ala	Phe	Ser
Arg	Ala 210	Gln	Pro	Gly	Ala	Ala 215	Pro	Gly	Ile	Tyr	Gln 220	Gln	Ser	Ala	Glu
Ala 225	Ser	Ser	Ser	Gln	Gly 230	Thr	Ala	Ala	Asn	Ser 235	Gln	Ser	Tyr	Thr	Ile 240
Met	Ser	Pro	Ala	Val 245	Leu	Lys	Ser	Glu	Leu 250	Gln	Ser	Pro	Thr	His 255	Pro
Ser	Ser	Ala	Leu 260	Pro	Pro	Ala	Thr	Ser 265	Pro	Thr	Ala	Gln	Glu 270	Ser	Tyr
Ser	Gln	туr 275	Pro	Val	Pro	Asp	Val 280	Ser	Thr	Tyr	Gln	Tyr 285	Asp	Glu	Thr
Ser	Gly 290	Tyr	Tyr	Tyr	Asp	Pro 295	Gln	Thr	Gly	Leu	Туг 300	Tyr	Asp	Pro	Asn
Ser 305	Gln	Tyr	Tyr	Tyr	Asn 310	Ala	Gln	Ser	Gln	Gln 315	Tyr	Leu	Tyr	Trp	Asp 320
Gly	Glu	Arg	Arg	Thr 325	Tyr	Val	Pro	Ala	Leu 330	Glu	Gln	Ser	Ala	Asp 335	Gly
His	Lys	Glu	Thr 340	Gly	Ala	Pro	Ser	Lys 345	Glu	Gly	Lys	Glu	Lys 350	Lys	Glu
Lys	His	Lys 355	Thr	Lys	Thr	Ala	Gln 360	Gln	Ile	Ala	Lys	Asp 365	Met	Glu	Arg

пр	370	ary	261	rea	ASII	375	GIII	пур	GIU	ASII	380	гур	ASII	261	File
Gln 385	Pro	Ile	Ser	Ser	Leu 390	Arg	Asp	Asp	Glu	Arg 395	Arg	Glu	Ser	Ala	Thr 400
Ala	Asp	Ala	Gly	Туг 405	Ala	Ile	Leu	Glu	Lys 410	Lys	Gly	Ala	Leu	Ala 415	Glu
Arg	Gln	His	Thr 420	Ser	Met	Asp	Leu	Pro 425	Lys	Leu	Ala	Ser	Asp 430	Asp	Arg
Pro	Ser	Pro 435	Pro	Arg	Xaa	Leu	Val 440	Ala	Ala	Tyr	Ser	Gly 445	Glu	Ser	Asp
Ser	Glu 450	Glu	Glu	Gln	Glu	Arg 455	Gly	Gly	Pro	Glu	Arg 460	Glu	Glu	Lys	Leu
Thr 465	Asp	Trp	Gln	Lys	Leu 470	Ala	Cys	Leu	Leu	Cys 475	Arg	Arg	Gln	Phe	Pro 480
Ser	Lys	Glu	Ala	Leu 485	Ile	Arg	His	Gln	Gln 490	Leu	Ser	Gly	Leu	His 495	Lys
Gln	Asn	Leu	Glu 500	Ile	His	Arg	Arg	Ala 505	His	Leu	Ser	Glu	Asn 510	Glu	Leu
Glu	Ala	Leu 515	Glu	Lys	Asn	Asp	Met 520	Glu	Gln	Met	Lys	Tyr 525	Arg	Asp	Arg
Ala	Ala 530	Glu	Arg	Arg	Glu	Lys 535	Tyr	Gly	Ile	Pro	Glu 540	Pro	Pro	Glu	Pro
545			-		Gly 550					555					560
				565	Gly				570					575	
Leu	Gln	Ala	Met 580	Gly	Trp	Lys	Glu	Gly 585	Ser	Gly	Leu	Gly	Arg 590	Lys	Lys
		595			Pro		600					605			
Gly	Leu 610	Gly	Ala	Arg	Gly	Ser 615	Ser	Tyr	Gly	Val	Thr 620	Ser	Thr	Glu	Ser
Tyr 625	Lys	Glu	Thr	Leu	His 630	Lys	Thr	Met	Val	Thr 635	Arg	Phe	Asn	Glu	Ala 640

616

Gln

<210> 653 <211> 516 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (1) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (247) <223> Kaa equals any of the naturally occurring L-amino acids <400> 653 Xaa Thr Arg Pro Gly Arg Gln Thr Arg Leu Cys Arg Pro Ala Ile Ser Leu Leu Trp Leu Val Thr Pro Gly Val Pro Ala Phe Ser Gly Trp Gly 25 30 Arg Arg His Arg Gly Arg Thr Gly Arg Arg Ala Met Ala Ser Cys Val Gly Ser Arg Thr Leu Ser Lys Asp Asp Val Asn Tyr Lys Met His Phe Arq Met Ile Asn Glu Gln Gln Val Glu Asp Ile Thr Ile Asp Phe Phe 65 Tyr Arg Pro His Thr Ile Thr Leu Leu Ser Phe Thr Ile Val Ser Leu Met Tyr Phe Ala Phe Thr Arg Asp Asp Ser Val Pro Glu Asp Asn Ile 105 Trp Arg Gly Ile Leu Ser Val Ile Phe Phe Phe Leu Ile Ile Ser Val 115 Leu Ala Phe Pro Asn Gly Pro Phe Thr Arg Pro His Pro Ala Leu Trp Arg Met Val Phe Gly Leu Ser Val Leu Tyr Phe Leu Phe Leu Val Phe 145 150 155

Leu	Leu	Phe	Leu	Asn 165	Phe	Glu	Gln	Val	Lys 170	Ser	Leu	Met	Tyr	175	Leu
Asp	Pro	Asn	Leu 180	Arg	туг	Ala	Thr	Arg 185	Glu	Ala	Asp	Val	Met 190	Glu	туг
Ala	Val	Asn 195	Cys	His	Val	Ile	Thr 200	Trp	Glu	Arg	Ile	Ile 205	Ser	His	Phe
Asp	Ile 210	Phe	Ala	Phe	Gly	His 215	Phe	Trp	Gly	Trp	Ala 220	Met	Lys	Ala	Leu
Leu 225	Ile	Arg	Ser	Tyr	Gly 230	Leu	Cys	Trp	Thr	Ile 235	Ser	Ile	Thr	Trp	Glu 240
Leu	Thr	Glu	Leu	Phe 245	Phe	Xaa	His	Leu	Leu 250	Pro	Asn	Phe	Ala	Glu 255	Cys
Trp	Trp	Asp	Gln 260	Val	Ile	Leu	Asp	Ile 265	Leu	Leu	Суз	Asn	Gly 270	Gly	Gly
Ile	Trp	Leu 275	Gly	Met	Val	Val	Cys 280	Arg	Phe	Leu	Glu	Met 285	Arg	Thr	Tyr
	290				-	295					300		Lys		_
305			•		310					315			Val		320
Phe	Asp	Pro	Lys	Ser 325	Ser	Phe	Gln	Arg	Val 330	Ala	Gly	Val	Tyr	1335	Phe
			340					345					Leu 350	_	
		355					360					365	Arg		
	370					375					380		Tyr		
385					390					395			Trp		400
				405					410	_			Phe	415	
Asp	Leu	Phe	Ser 420	Lys	Thr	Gln	Ile	Leu 425	Tyr	Val	Val	Leu	Trp 430	Leu	Leu

PCT/US00/05881 WO 00/55173

618

Cys Val Ala Phe Thr Thr Phe Leu Cys Leu Tyr Gly Met Ile Trp Tyr 435 440

Ala Glu His Tyr Gly His Arg Glu Lys Thr Tyr Ser Glu Cys Glu Asp 455

Gly Thr Tyr Ser Pro Glu Ile Ser Trp His His Arg Lys Gly Thr Lys 470 475

Gly Ser Glu Asp Ser Pro Pro Lys His Ala Gly Asn Asn Glu Ser His

Ser Ser Arg Arg Arg Asn Arg His Ser Lys Ser Lys Val Thr Asn Gly 505

Val Gly Lys Lys 515

<210> 654

<211> 663

<212> PRT

<213> Homo sapiens

<400> 654

Leu Glu Cys Arg Glu Ala His Ile Arg Asp Val Pro Val Val Arg Leu

Pro Ala Asp Ser Pro Ile Pro Glu Arg Gly Asp Leu Ser Cys Arg Met 20

His Thr Cys Phe Asp Val Tyr Arg Cys Gly Phe Asn Pro Lys Asn Lys

Ile Lys Val Tyr Ile Tyr Ala Leu Lys Lys Tyr Val Asp Asp Phe Gly 60 55 50

Val Ser Val Ser Asn Thr Ile Ser Arg Glu Tyr Asn Glu Leu Leu Met 70

Ala Ile Ser Asp Ser Asp Tyr Tyr Thr Asp Asp Ile Asn Arg Ala Cys 90

Leu Phe Val Pro Ser Ile Asp Val Leu Asn Gln Asn Thr Leu Arg Ile 100 105

Lys Glu Thr Ala Gln Ala Met Ala Gln Leu Ser Arg Trp Asp Arg Gly 120

Thr Asn His Leu Leu Phe Asn Met Leu Pro Gly Gly Pro Pro Asp Tyr

PCT/US00/05881

	130					135					140				
Asn 145	Thr	Ala	Leu	Asp	Val 150	Pro	Arg	Asp	Arg	Ala 155	Leu	Leu	Ala	Gly	Gly 160
Gly	Phe	Ser	Thr	Trp 165	Thr	туг	Arg	Gln	Gly 170	туг	Asp	Val	Ser	Ile 175	Pro
Val	Tyr	Ser	Pro 180	Leu	Ser	Ala	Glu	Val 185	Asp	Leu	Pro	Glu	Lys 190	Gly	Pro
Gly	Pro	Arg 195	Gln	Tyr	Phe	Leu	Leu 200	Ser	Ser	Gln	Val	Gly 205	Leu	His	Pro
Glu	Туг 210	Arg	Glu	Asp	Leu	Glu 215	Ala	Leu	Gln	Val	Lys 220	His	Gly	Glu	Ser
Val 225	Leu	Val	Leu	Asp	Lys 230	Cys	Thr	Asn	Leu	Ser 235	Glu	Gly	Val	Leu	Ser 240
Val	Arg	Lys	Arg	Cys 245	His	Lys	His	Gln	Val 250	Phe	Asp	Tyr	Pro	Gln 255	Val
Leu	Gln	Glu	Ala 260	Thr	Phe	Cys	Val	Val 265	Leu	Arg	Gly	Ala	Arg 270	Leu	Gly
Gln	Ala	Val 275	Leu	Ser	Asp	Val	Leu 280	Gln	Ala	Gly	Cys	Val 285	Pro	Val	Val
Ile	Ala 290	Asp	Ser	Tyr	Ile	Leu 295	Pro	Phe	Ser	Glu	Val 300	Leu	Asp	Trp	Lys
Arg 305	Ala	Ser	Val	Val	Val 310	Pro	Glu	Glu	Lys	Met 315	Ser	Asp	Val	туr	ser 320
Ile	Leu	Gln	Ser	Ile 325	Pro	Gln	Arg	Gln	Ile 330	Glu	Glu	Met	Gln	Arg 335	Gln
Ala	Arg	Trp	Phe 340	Trp	Glu	Ala	Tyr	Phe 345	Gln	Ser	Ile	Lys	Ala 350	Ile	Ala
Leu	Ala	Thr 355	Leu	Gln	Ile	Ile	Asn 360	Asp	Arg	Ile	Tyr	Pro 365	Tyr	Ala	Ala
Ile	Ser 370	Tyr	Glu	Glu	Trp	Asn 375	Asp	Pro	Pro	Ala	Val 380	Lys	Trp	Gly	Ser
Val 385	Ser	Asn	Pro	Leu	Phe 390	Leu	Pro	Leu	Ile	Pro 395	Pro	Gln	Ser	Gln	Gly 400
Phe	Thr	Ala	Ile	Val	Leu	Thr	Tyr	Asp	Arg	Val	Glu	Ser	Leu	Phe	Arg

				405					410					415	
Val	Ile	Thr	Glu 420	Val	Ser	Lys	Val	Pro 425	Ser	Leu	Ser	Lys	Leu 430	Leu	Val
Val	Trp	Asn 435	Asn	Gln	Asn	Lys	Asn 440	Pro	Pro	Glu	Asp	Ser 445	Leu	Trp	Pro
Lys	Ile 450	Arg	Val	Pro	Leu	Lys 455	Val	Val	Arg	Thr	Ala 460	Glu	Asn	Lys	Leu
Ser 465	Asn	Arg	Phe	Phe	Pro 470	Tyr	Asp	Glu	Ile	Glu 475	Thr	Glu	Ala	Val	Leu 480
Ala	Ile	Asp	Asp	Asp 485	Ile	Ile	Met	Leu	Thr 490	Ser	Asp	Glu	Leu	Gln 495	Phe
Gly	Tyr	Glu	Val 500	Trp	Arg	Glu	Phe	Pro 505	Asp	Arg	Leu	Val	Gly 510	Tyr	Pro
Gly	Arg	Leu 515	His	Leu	Trp	Asp	His 520	Glu	Met	Asn	Lys	Trp 525	Lys	туг	Glu
Ser	Glu 530	Trp	Thr	Asn	Glu	Val 535	Ser	Met	Val	Leu	Thr 540	Gly	Ala	Ala	Phe
Tyr 545	His	Lys	Tyr	Phe	Asn 550	Tyr	Leu	Tyr	Thr	Tyr 555	Lys	Met	Pro	Gly	Asp 560
Ile	Lys	Asn	Trp	Val 565	Asp	Ala	His	Met	Asn 570	Суз	Glu	Asp	Ile	Ala 575	Met
Asn	Phe	Leu	Val 580	Ala	Asn	Val	Thr	Gly 585	Lys	Ala	Val	Ile	Lys 590	Val	Thr
Pro	Arg	Lys 595	Lys	Phe	Lys	Cys	Pro 600	Glu	Cys	Thr	Ala	Ile 605	Asp	Gly	Leu
Ser	Leu 610	Asp	Gln	Thr	His	Met 615	Val	Glu	Arg	Ser	Glu 620	Cys	Ile	Asn	Lys
Phe 625	Ala	Ser	Val	Phe	Gly 630	Thr	Met	Pro	Leu	Lys 635	Val	Val	Glu	His	Arg 640
Ala	Asp	Pro	Val	Leu 645	Tyr	Lys	Asp	Asp	Phe 650	Pro	Glu	.Lys	Leu	Lys 655	Ser
Phe	Pro	Asn	Ile	Gly	Ser	Leu									

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<210> 655
<211> 97
<212> PRT
<213> Homo sapiens
<220>
<221> SITE
<222> (38)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (91)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 655
Ala Thr Gln Leu Leu Ser Ser Phe Ser Val Gly Pro Leu Leu Gln Ile
                                     10
Thr Phe Tyr Glu Asp Lys Asn Phe Gln Gly Arg Arg Tyr Asp Cys Asp
             20
                                 25
Cys Asp Cys Ala Asp Xaa His Thr Tyr Leu Ser Arg Cys Asn Ser Ile
Lys Val Glu Gly Gly Thr Trp Ala Val Tyr Glu Arg Pro Asn Phe Ala
                         55
Gly Tyr Met Tyr Ile Leu Pro Gln Gly Glu Tyr Pro Glu Tyr Gln Arg
65
                     70
                                         75
Trp Met Gly Leu Asn Asp Arg Leu Ser Ser Xaa Arg Ala Val Ser Ser
                 85
                                     90
Ala
<210> 656
<211> 167
<212> PRT
<213> Homo sapiens
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<222> (59)
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<223> Xaa equals any of the naturally occurring L-amino acids

<220>

622

<221> SITE

<222> (73)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 656

Asp Ala Asp Leu Val Ile Trp Asp Pro Asp Ser Val Lys Thr Ile Ser 1 10 15

Ala Lys Thr His Asn Ser Ser Leu Glu Tyr Asn Ile Phe Glu Gly Met
20 25 30

Glu Cys Arg Gly Ser Pro Leu Val Val Ile Ser Gln Gly Lys Ile Val
35 40 45

Leu Glu Asp Gly Thr Leu His Val Thr Glu Xaa Ser Gly Arg Tyr Ile
50 55 60

Pro Arg Lys Pro Phe Pro Asp Phe Xaa Tyr Lys Arg Ile Lys Ala Arg 65 70 75 80

Ser Arg Leu Ala Glu Leu Arg Gly Val Pro Arg Gly Leu Tyr Asp Gly 85 90 95

Pro Val Cys Glu Val Ser Val Thr Pro Lys Thr Val Thr Pro Ala Ser

Ser Ala Lys Thr Ser Pro Ala Lys Gln Gln Ala Pro Pro Val Arg Asn 115 120 125

Leu His Gln Ser Gly Phe Ser Leu Ser Gly Ala Gln Ile Asp Asp Asn 130 135 140

Ile Pro Arg Arg Thr Thr Gln Arg Ile Val Ala Pro Pro Gly Gly Arg 145 150 155 160

Ala Asn Ile Thr Ser Leu Gly 165

<210> 657

<211> 176

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (1)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

623

<221> SITE <222> (6)

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<220>

<221> SITE

<222> (26)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 657

Xaa Ser Leu Asn Leu Xaa Lys Leu Ala Leu His Arg Gly Gly Gly Arg

1 5 10 15

Ser Arg Thr Ser Gly Ser Pro Gly Leu Kaa Glu Phe Gly Thr Ser Ala 20 25 30

Val Leu Leu Arg Leu Gly Asp Glu Leu Glu Met Ile Arg Pro Ser Val 35 40 45

Tyr Arg Asn Val Ala Arg Gln Leu His Ile Ser Leu Gln Ser Glu Pro 50 60

Val Val Thr Asp Ala Phe Leu Ala Val Ala Gly His Ile Phe Ser Ala 65 70 75 80

Gly Ile Thr Trp Gly Lys Val Val Ser Leu Tyr Ala Val Ala Ala Gly 85 90 95

Leu Ala Val Asp Cys Val Arg Gln Ala Gln Pro Ala Met Val His Ala 100 105 110

Leu Val Asp Cys Leu Gly Glu Phe Val Arg Lys Thr Leu Ala Thr Trp
115 120 125

Leu Arg Arg Gly Gly Trp Thr Asp Val Leu Lys Cys Val Val Ser 130 135 140

Thr Asp Pro Gly Leu Arg Ser His Trp Leu Val Ala Ala Leu Cys Ser 145 150 155 160

Phe Gly Arg Phe Leu Lys Ala Ala Phe Phe Val Leu Leu Pro Glu Arg 165 170 175

<210> 658

<211> 137

<212> PRT

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<213> Homo sapiens
<220>
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<220>
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<222> (91)
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<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (124)
<223> Xaa equals any of the naturally occurring L-amino acids
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<222> (129)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (131)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 658
Gly Pro Val Gly Ser Ser Ser Glu Ala Pro Arg Gly Ala Gly Asp Ala
                                     10
Gly Met Ala Gly Glu Leu Thr Pro Glu Glu Glu Ala Gln Tyr Lys Lys
Ala Phe Ser Ala Val Asp Thr Asp Gly Asn Gly Thr Ile Asn Ala Gln
                             40
Glu Leu Gly Ala Ala Leu Lys Ala Thr Gly Lys Asn Leu Ser Glu Ala
     50
                         55
                                             60
Gln Leu Arg Lys Leu Ile Ser Glu Val Asp Xaa Asp Gly Asp Gly Glu
Ile Ser Phe Gln Glu Phe Leu Thr Ala Ala Xaa Lys Ala Arg Ala Gly
                 85
                                     90
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625

Leu Glu Asp Leu Xaa Val Ala Phe Arg Ala Phe Asp Gln Asp Gly Asp 100 105 110 Gly His Ile Thr Val Asp Glu Leu Arg Arg Ala Xaa Ala Gly Leu Gly Xaa Leu Xaa Glu Ile Asp His Phe Gly <210> 659 <211> 34 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (2) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (28) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (30) <223> Xaa equals any of the naturally occurring L-amino acids <400> 659 Pro Xaa Ser Arg Gln Asp Val Met Asp Ile Val Phe Ile Glu Gln Leu Ser Val Ile Thr Thr Ile Gly Val Tyr Asp Trp Xaa Gln Xaa Ser Asn 25 Arg Ser <210> 660 <211> 56 <212> PRT <213> Homo sapiens

Asn Pro Ile Ser Pro Lys Asn Tyr Lys Lys Ile Ser Gln Ala Gln Ser

10

5

<400> 660

Gln Leu Pro Val Ile Pro Ala Thr Gln Glu Ala Glu Ser Gly Glu Ser Leu Gly Pro Gly Ala Ala Glu Val Asn Ser Glu Pro Arg Leu His His 40 Arg Thr Pro Ala Trp Ile Thr Lys 50 <210> 661 <211> 41 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (29) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (31) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (36) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (39) <223> Xaa equals any of the naturally occurring L-amino acids Tyr Ile Gly Phe Val Ile Leu Val Phe Phe Ala Ser Ser Tyr Val Lys 10 Glu Ile Asp Asn Lys Ile Leu Asn Asn Lys Lys Xaa Lys Xaa Ser

<210> 662 <211> 524

35

Ser Lys Gly Xaa Val Ala Xaa Ala Ile

627

<212> PRT <213> Homo sapiens <220> <221> SITE <222> (124) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (191) <223> Kaa equals any of the naturally occurring L-amino acids Cys Glu Ala Trp Arg Gly Arg Ala Asp Pro Gly Gly Gln Ser Cys Leu Gln Ala Leu Gln Asn Ser Thr Ala Pro Gln His Pro Gly Leu His Arg 25 Trp Thr Gly Asp Arg Lys Met Pro Pro Arg Arg Asp Arg Gly Cys Asp 35 Pro Val Gly Asn Ile Pro Gln Gly Glu Ser Gly Gly Trp Trp Pro Glu Gly Ala Gly Asp Leu Leu Gly Ala Thr Pro Asp Arg Glu Ser Pro Gln Leu Pro Gly Gln Arg Leu Gln Pro His Pro Gln Gln Cys Leu His Gly Arg Arg Val Arg Gly Pro Ser Trp Arg Val Glu Ala Trp Gly Pro Gly Leu His Val Phe Gly Pro Gly Gln Arg Trp Gly Xaa Ser Pro Gln Gly 115 120

Gly Arg Val Val Arg Glu Lys Trp Ser Ala Asp Met Trp Arg Leu Gly
145 150 155 160

Ile Pro Glu Leu Glu Gln Tyr Asp Pro Pro Glu Leu Ala Asp Ser Ser

135

Cys Leu Ile Trp Glu Val Phe Asn Gly Pro Leu Pro Arg Ala Ala Ala 165 170 175

Leu Arg Asn Pro Gly Lys Ile Pro Lys Thr Leu Val Pro His Xaa Cys 180 185 190

Lys Leu Val Gly Ala Asn Pro Lys Val Arg Pro Asn Pro Ala Arg Phe

PCT/US00/05881

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		195					200					205			
Leu	Gln 210	Asn	Cys	Arg	Ala	Pro 215	Gly	Gly	Phe	Met	Ser 220	Asn	Arg	Phe	Val
Glu 225	Thr	Asn	Leu	Phe	Leu 230	Glu	Glu	Ile	Gln	Ile 235	Lys	Glu	Pro	Ala	Glu 240
Lys	Gln	Lys	Phe	Phe 245	Gln	Glu	Leu	Ser	Lys 250	Ser	Leu	Asp	Ala	Phe 255	Pro
Glu	Asp	Phe	Cys 260	Arg	His	Lys	Val	Leu 265	Pro	Gln	Leu	Leu	Thr 270	Ala	Phe
Glu	Phe	Gly 275	Asn	Ala	Gly	Ala	Val 280	Val	Leu	Thr	Pro	Leu 285	Phe	Lys	Val
Gly	Lys 290	Phe	Leu	Ser	Ala	Glu 295	Glu	Tyr	Gln	Gln	Lys 300	Ile	Ile	Pro	Val
Val 305	Val	Lys	Met	Phe	Ser 310	Ser	Thr	Asp	Arg	Ala 315	Met	Arg	Ile	Arg	Leu 320
Leu	Gln	Gln	Met	Glu 325	Gln	Phe	Ile	Gln	Tyr 330	Leu	Asp	Glu	Pro	Thr 335	Val
Asn	Thr	Gln	Ile 340	Phe	Pro	His	Val	Val 345	His	Gly	Phe	Leu	Asp 350	Thr	Asn
Pro		Ile .355	Arg	Glu	Gln	Thr	Val 360	Lys	Ser	Met	Leu	Leu 365	Leu	Ala	Pro
Lys	Leu 370	Asn	Glu	Ala	Asn	Leu 375	Asn	Val	Glu	Leu	Met 380	Lys	His	Phe	Ala
Arg 385	Leu	Gln	Ala	Lys	Asp 390	Glu	Gln	Gly	Pro	11e 395	Arg	Cys	Asn	Thr	Thr 400
Val	Cys	Leu	Gly	Lys 405	Ile	Gly	Ser	Tyr	Leu 410	Ser	Ala	Ser	Thr	Arg 415	His
Arg	Val	Leu	Thr 420	Ser	Ala	Phe	Ser-	Arg 425	Ala	Thr	Arg	Asp	Pro 430	Phe	Ala
Pro	Ser	Arg 435	Val	Ala	Gly	Val	Leu 440	Gly	Phe	Ala	Ala	Thr 445	His	Asn	Leu
Tyr	Ser 450	Met	Asn	Asp	Cys	Ala 455	Gln	Lys	Ile	Leu	Pro 460	Val	Leu	Cys	Gly
Leu	Thr	Val	Asp	Pro	Glu	Lys	Ser	Val	Arq	Asp	Gln	Ala	Phe	Lys	Ala

480 470 475 465 Phe Gly Ala Ser Cys Pro Asn Trp Ser Leu Cys Arg Arg Thr Arg Pro 485 Ser Trp Arg Lys Trp Arg Arg Met Ser Met Gln Pro Pro Ala Leu Ala 505 500 Trp Glu Glu Pro Gln Leu Ala Gly Gln Ala Gly Pro 520 <210> 663 <211> 272 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (29) <223> Xaa equals any of the naturally occurring L-amino acids <400> 663 Pro Thr Leu Asp Ser Ala Arg Ser Leu Ser Met Arg Ala Pro Ser Leu 5 10 Thr Pro Ser Ala Ala Pro Leu Ser Thr Trp Pro Leu Xaa Ile Leu Val Arg Ser Gly His Asn Arg Ala Val Asp Trp Trp Ser Leu Gly Ala Leu Met Tyr Asp Met Leu Thr Gly Ser Pro Pro Phe Thr Ala Glu Asn Arg Lys Lys Thr Met Asp Lys Ile Ile Arg Gly Lys Leu Ala Leu Pro Pro 70 Tyr Leu Thr Pro Asp Ala Arg Asp Leu Val Lys Lys Phe Leu Lys Arg 90 Asn Pro Ser Gln Arg Ile Gly Gly Gly Pro Gly Asp Ala Ala Asp Val 100 Gln Arg His Pro Phe Phe Arg His Met Asn Trp Asp Asp Leu Leu Ala 120 Trp Arg Val Asp Pro Pro Phe Arg Pro Cys Leu Gln Ser Glu Glu Asp

135

630

Val Ser Gln Phe Asp Thr Arg Phe Thr Arg Gln Thr Pro Val Asp Ser 155 145 150 Pro Asp Asp Thr Ala Leu Ser Glu Ser Ala Asn Gln Ala Phe Leu Gly 165 170 Phe Thr Tyr Val Ala Pro Ser Val Leu Asp Ser Ile Lys Glu Gly Phe 185 Ser Phe Gln Pro Lys Leu Arg Ser Pro Arg Arg Leu Asn Ser Ser Pro 195 200 Arg Ala Pro Val Ser Pro Leu Lys Phe Ser Pro Phe Glu Gly Phe Arg 215 Pro Ser Pro Ser Leu Pro Glu Pro Thr Glu Leu Pro Leu Pro Pro Leu 225 230 235 Leu Pro Pro Pro Pro Pro Ser Thr Thr Ala Pro Leu Pro Ile Arg Pro 245 250 Pro Ser Gly Thr Lys Lys Ser Lys Arg Gly Arg Gly Arg Pro Gly Arg

265

<210> 664

<211> 256

<212> PRT

<213> Homo sapiens

260

<220>

<221> SITE

<222> (99)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 664

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1 5 10 15

Leu Leu Ser Asp Gln Gly Tyr Arg Val Asp Gly Arg Arg Ala Gly Glu
20 25 30

Leu Arg Lys Ile Gln Ala Arg Met Gly Val Phe Ala Gln Ala Asp Gly 35 40 45

Ser Ala Tyr Ile Glu Gln Gly Asn Thr Lys Ala Leu Ala Val Val Tyr 50 60

Gly 65	Pro	His	Glu	Ile	Arg 70	Gly	Ser	Arg	Ala	Arg 75	Ala	Leu	Pro	Asp	Arg 80
Ala	Leu	Val	Asn	Cys 85	Gln	Tyr	Ser	Ser	Ala 90	Thr	Phe	Ser	Thr	Gly 95	Glu
Arg	Lys	Xaa	Arg 100	Pro	His	Gly	Asp	Arg 105	Lys	Ser	Cys	Glu	Met 110	Gly	Leu
Gln	Leu	Arg 115	Gln	Thr	Phe	Glu	Ala 120	Ala	Ile	Leu	Thr	Gln 125	Leu	His	Pro
Arg	Ser 130	Gln	Ile	Asp	Ile	Tyr 135	Val	Gln	Val	Leu	Gln 140	Ala	Asp	Gly	Gly
Thr 145	Tyr	Ala	Ala	Cys	Val 150	Asn	Ala	Ala	Thr	Leu 155	Ala	Val	Leu	Asp	Ala 160
Gly	Ile	Pro	Met	Arg 165	Asp	Phe	Val	Cys	Ala 170	Суз	Ser	Ala	Gly	Phe 175	Val
Asp	Gly	Thr	Ala 180	Leu	Ala	Asp	Leu	Ser 185	His	Val	Glu	Glu	Ala 190	Ala	Gly
Gly	Pro	Gln 195	Leu	Ala	Leu	Ala	Leu 200	Leu	Pro	Ala	Ser	Gly 205	Gln	Ile	Ala
Leu	Leu 210	Glu	Met	Asp	Ala	Arg 215	Leu	His	Glu	Asp	His 220	Leu	Glu	Arg	Val
Leu 225	Glu	Ala	Ala	Ala	Gln 230	Ala	Ala	Arg	Asp	Val 235	His	Thr	Leu	Leu	Asp 240
Arg	Val	Val	Arg	Gln 245	His	Val	Arg	Glu	Ala 250	Ser	Ile	Leu	Leu	Gly 255	Asp

<210> 665

<211> 241

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (9)

<223> Xaa equals any of the naturally occurring L-amino acids

<220)>														
<22	1> S	ITE													
<22	2> (122)													
<223	3> X	aa e	qual	s an	y of	the	nati	ural:	ly o	ccur	ring	L-a	mino	acio	is
<406)> 60	65													
Pro 1	Arg	Gly	Asp	Lys 5	Ala	Arg	Thr	Xaa	Pro 10	Pro	Ala	Ala	Ser	Ala 15	Arg
Pro	Ser	Arg	Ser 20	Lys	Arg	Gly	Gly	Glu 25	Glu	Arg	Val	Leu	Glu 30	Lys	Glü
Glu	Glu	Glu 35	Asp	Asp	Asp	Glu	Asp 40	Glu	Asp	Glu	Glu	Asp 45	Asp	Val	Ser
Glu	Gly 50	Ser	Glu	Val	Pro	Glu 55	Ser	Asp	Arg	Pro	Ala 60	Gly	Ala	Gln	His
His 65	Gln	Leu	Asn	Gly	Glu 70	Arg	Gly	Pro	Gln	Ser 75	Ala	Lys	Glu	Arg	Val
Lys	Glu	Trp	Thr	Pro , 85	Суѕ	Gly	Pro	His	Gln 90	Gly	Gln	Asp	Glu	Gly 95	Arg
Gly	Pro	Ala	Pro 100	Gly	Ser	Gly	Thr	Arg 105	Gln	Val	Phe	Ser	Met 110	Ala	Ala
Met	Asn	Lys 115	Glu	Gly	Gly	Thr	Ala 120	Ser	Xaa	Ala	Thr	Gly 125	Pro	Asp	Ser
Pro	Ser 130	Pro	Val	Pro	Leu	Pro 135	Pro	Gly	Lys	Pro	Ala 140	Leu	Pro	Gly	Ala
Asp 145	Gly	Thr	Pro	Phe	Gly 150	Cys	Pro	Pro	Gly	Arg 155	Lys	Glu	Lys	Pro	Ser 160
Asp	Pro	Val	Glu	Trp 165	Thr	Val	Met	Asp	Val 170	Val	Glu	Tyr	Phe	Thr 175	Glu
Ala	Gly	Phe	Pro 180	Glu	Gln	Ala	Thr	Val 185	Phe	Gln	Glu	Gln	Glu 190	Ile	Asp
Gly	Lys	Ser 195	Leu	Leu	Leu	Met	Gln 200	Arg	Thr	Asp	Val	Leu 205	Thr	Gly	Leu
Ser	Ile 210	Arg	Leu	Gly	Pro	Ala 215	Leu	Lys	Ile	туг	Glu 220	His	His	Ile	Lys
Val 225	Leu	Gln	Gln	Gly	His 230	Phe	Glu	Asp	Asp	Asp 235	Pro	Asp	Gly	Phe	Leu 240

633

Gly

<210> 666

<211> 131

<212> PRT

<213> Homo sapiens

<400> 666

Val Thr Gly Gly Gly Ala Val Leu Gly Ala Glu Ser His Ala Ser
1 5 10 15

Lys Asp Val Ala Ile Asp Met Met Asp Ser Arg Thr Ser Gln Gln Leu 20 25 30

Gln Leu Ile Asp Glu Gln Asp Ser Tyr Ile Gln Ser Arg Ala Asp Thr 35 40 45

Met Gln Asn Ile Glu Ser Thr Ile Val Glu Leu Gly Ser Ile Phe Gln 50 55 60

Gln Leu Ala His Met Val Lys Glu Gln Glu Glu Thr Ile Gln Arg Ile 65 70 75 80

Asp Glu Asn Val Leu Gly Ala Gln Leu Asp Val Glu Ala Ala His Ser 85 90 95

Glu Ile Leu Lys Tyr Phe Gln Ser Val Thr Ser Asn Arg Trp Leu Met 100 105 110

Val Lys Ile Phe Leu Ile Leu Ile Val Phe Phe Ile Ile Phe Val Val 115 120 125

Phe Leu Ala 130

<210> 667

<211> 652

<212> PRT

<213> Homo sapiens

<400> 667

Leu Ser Trp Asn Arg Tyr Thr Ser Val Ser Pro Leu His Arg Ser Leu

1 5 10 15

Gln Leu Pro Pro Arg Val Ser Gly Val Arg Cys Asp Gln Cys Ala Arg

			20					25					30		
Gly	Phe	Ser 35	Gly	Ile	Phe	Pro	Ala 40	Суз	His	Pro	Cys	His 45	Ala	Cys	Phe
Gly	Asp 50	Trp	Asp	Arg	Val	Val 55	Gln	Asp	Leu	Ala	Ala 60	Arg	Thr	Gln	Arg
Leu 65	Glu	Gln	Arg	Ala	Gln 70	Glu	Leu	Gln	Gln	Thr 75	Gly	Val	Leu	Gly	Ala 80
Phe	Glu	Ser	Ser	Phe 85	Trp	His	Met	Gln	Glu 90	Lys	Leu	Gly	Ile	Val 95	Gln
Gly	Ile	Val	Gly 100	Ala	Arg	Asn	Thr	Ser 105	Ala	Ala	Ser	Thr	Ala 110	Gln	Leu
Val	Glu	Ala 115	Thr	Glu	Glu	Leu	Arg 120	Arg	Glu	Ile	Gly	Glu 125	Ala	Thr	Glu
His	Leu 130	Thr	Gln	Leu	Glu	Ala 135	Asp	Leu	Thr	Asp	Val 140	Gln	Asp	Glu	Asn
Phe 145	Asn	Ala	Asn	His	Ala 150	Leu	Ser	Gly	Leu	Glu 155	Arg	Asp	Arg	Leu	Ala 160
Leu	Asn	Leu	Thr	Leu 165	Arg	Gln	Leu	Asp	Gln 170	His	Leu	Asp	Leu	Leu 175	Lys
His	Ser	Asn	Phe 180	Leu	Gly	Ala	туг	Asp 185	Ser	Ile	Arg	His	Ala 190	His	Ser
Gln	Ser	Ala 195	Glu	Ala	Glu	Arg	Arg 200	Ala	Asn	Thr	Ser	Ala 205	Leu	Ala	Val
Pro	Ser 210	Pro	Val	Ser	Asn	Ser 215	Ala	Ser	Ala	Arg	His 220	Arg	Thr	Glu	Ala
Leu 225	Met	Asp	Ala		Lys 230	Glu	Asp	Phe		Ser 235		His	Met		Asn 240
Gln	Arg	Ala	Leu	Gly 245	Lys	Leu	Ser	Ala	His 250	Thr	His	Thr	Leu	Ser 255	Leu
Thr	Asp	Ile	Asn 260	Glu	Leu	Val	Cys	Gly 265	Ala	Pro	Gly	Asp	Ala 270	Pro	Суз
Ala	Thr	Ser 275	Pro	Cys	Gly	Gly	Ala 280	Gly	Cys	Arg	Asp	Glu 285	Asp	Gly	Gln
Pro	Arg	Cys	Gly	Gly	Leu	Ser	Суз	Asn	Gly	Ala	Ala	Ala	Thr	Ala	Asp

	290					293					300				
Leu 305	Ala	Leu	Gly	Arg	Ala 310	Arg	His	Thr	Gln	Ala 315	Glu	Leu	Gln	Arg	Ala 320
Leu	Ala	Glu	Gly	Gly 325	Ser	Ile	Leu	Ser	Arg 330	Val	Ala	Glu	Thr	Arg 335	Arg
Gln	Ala	Ser	Glu 340	Ala	Gln	Gln	Arg	Ala 345	Gln	Ala	Ala	Leu	Asp 350	Lys	Ala
Asn	Ala	Ser 355	Arg	Gly	Gln	Val	Glu 360	Gln	Ala	Asn	Gln	Glu 365	Leu	Gln	Glu
Leu	11e 370	Gln	Ser	Val	Lys	Asp 375	Phe	Leu	Asn	Gln	Glu 380	Gly	Ala	Asp	Pro
Asp 385	Ser	Ile	Glu	Met	Val 390	Ala	Thr	Arg	Val	Leu 395	Glu	Leu	Ser	Ile	Pro 400
Ala	Ser	Ala	Glu	Gln 405	Ile	Gln	His	Leu	Ala 410	Gly	Ala	Ile	Ala	Glu 415	Arg
Val	Arg	Ser	Leu 420	Ala	Asp	Val	Asp	Ala 425	Ile	Leu	Ala	Arg	Thr 430	Val	Gly
Asp	Val	Arg 435	Arg	Ala	Glu	Gln	Leu 440	Leu	Gln	Asp	Ala	Arg 445	Arg	Ala	Arg
Ser	Trp 450	Ala	Glu	Asp	Glu	Lys 455	Gln	Lys	Ala	Glu	Thr 460	Val	Gln	Ala	Ala
Leu 465	Glu	Glu	Ala	Gln	Arg 470	Ala	Gln	Gly	Ile	Ala 475	Gln	Gly	Ala	Ile	Arg 480
Gly	Ala	Val	Ala	Asp 485	Thr	Arg	Asp	Thr	Glu 490	Gln	Thr	Leu	Tyr	Gln 495	Val
Gln	Glu	Arg	Met 500	Ala	Gly	Ala	Glu	-		Leu		Ser	Ala 510	Gly	Glu
Arg	Ala	Arg 515	Gln	Leu	Asp	Ala	Leu 520	Leu	Glu	Ala	Leu	Lys 525	Leu	Lys	Arg
Ala	Gly 530	Asn	Ser	Leu	Ala	Ala 535	Ser	Thr	Ala	Glu	Glu 540	Thr	Ala	Gly	Ser
Ala 545	Gln	Gly	Arg	Ala	Gln 550	Glu	Ala	Glu	Gln	Leu 555	Leu	Arg	Gly	Pro	Leu 560
Gly	Asp	Gln	Tyr	Gln	Thr	Val	Lys	Ala	Leu	Ala	Glu	Arg	Lys	Ala	Gln

PCT/US00/05881 WO 00/55173

636

570 575 565

Gly Val Leu Ala Ala Gln Ala Arg Ala Glu Gln Leu Arg Asp Glu Ala 585

Arg Asp Leu Leu Gln Ala Ala Gln Asp Lys Leu Gln Arg Leu Gln Glu 600

Leu Glu Gly Thr Tyr Glu Glu Asn Glu Arg Ala Leu Glu Ser Lys Ala 615

Ala Gln Leu Asp Gly Leu Glu Ala Arg Met Arg Ser Val Leu Gln Ala 625 630 635

Ile Asn Leu Gln Val Gln Ile Tyr Asn Thr Cys Gln 645

<210> 668

<211> 406

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (84)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 668

Gly Ala Val Arg Ser Ser Cys Ala Glu Leu Gln Ala Arg Val Met Ala 10

Ala Leu Arg Gln Pro Gln Val Ala Glu Cys Trp Pro Arg Pro Gly Glu

Pro Ser Gly Arg Ser Ser Gly Pro Ser Pro Ser Trp Pro Cys Gln Arg 40

Arg Ala Ala Cys Asn Leu Ile Gly Glu His Thr Asp Tyr Asn Gln Gly 55

Leu Val Leu Pro Met Ala Leu Glu Leu Met Thr Val Leu Val Gly Ser 70 75

Pro Arg Lys Xaa Gly Leu Val Ser Leu Leu Thr Thr Ser Glu Gly Ala 90

Asp Glu Pro Gln Arg Leu Gln Phe Pro Leu Pro Thr Ala Gln Arg Ser 105 100

Leu	Glu	Pro 115	Gly	Thr	Pro	Arg	Trp 120	Ala	Asn	Tyr	Val	Lys 125	Gly	Val	Ile
Gln	Туг 130	Tyr	Pro	Ala	Ala	Pro 135	Leu	Pro	Gly	Phe	ser 140	Ala	Val	Val	Val
Ser 145	Ser	Val	Pro	Leu	Gly 150	Gly	Gly	Leu	Ser	Ser 155	Ser	Ala	Ser	Leu	Glu 160
Val	Ala	Thr	туг	Thr 165	Phe	Leu	Gln	Gln	Leu 170	Суз	Pro	Asp	Ser	Gly 175	Thr
Ile	Ala	Ala	Arg 180	Ala	Gln	Val	Суз	Gln 185	Gln	Ala	Glu	His	Ser 190	Phe	Ala
Gly	Met	Pro 195	Cys	Gly	Ile	Met	Asp 200	Gln	Phe	Ile	Ser	Leu 205	Met	Gly	Gln
Lys	Gly 210	His	Ala	Leu	Leu	Ile 215	Asp	Cys	Arg	Ser	Leu 220	Glu	Thr	Ser	Leu
Val 225	Pro	Leu	Ser	Asp	Pro 230	Lys	Leu	Ala	Val	Leu 235	Ile	Thr	Asn	Ser	Asn 240
Val	Arg	His	Ser	Leu 245	Ala	Ser	Ser	Glu	Туг 250	Pro	Val	Arg	Arg	Arg 255	Gln
Cys	Glu	Glu	Val 260	Ala	Arg	Ala	Leu	Gly 265	Lys	Glu	Ser	Leu	Arg 270	Glu	Val
Gln	Leu	Glu 275	Glu	Leu	Glu	Ala	Ala 280	Arg	Asp	Leu	Val	Ser 285	Lys	Glu	Gly
Phe	Arg 290	Arg	Ala	Arg	His	Val 295	Val	Gly	Glu	Ile	Arg 300	Arg	Thr	Ala	Gln
Ala 305	Ala	Ala	Ala	Leu	Arg 310	Arg	Gly	Asp	Tyr	Arg 315	Ala	Phe	Gly	Arg	Leu 320
Met	Val	Glu	Ser	His 325	Arg	Ser	Leu	Arg	Asp 330	Asp	Tyr	Glu	Val	Ser 335	Cys
Pro	Glu	Leu	Asp 340	Gln	Leu	Val	Glu	Ala 345	Ala	Leu	Ala	Val	Pro 350	Ġly	Val
Tyr	Gly	Ser 355	Arg	Met	Thr	Gly	Gly 360	Gly	Phe	Gly	Gly	Cys 365	Thr	Val	Thr
Leu	Leu 370	Glu	Ala	Ser	Ala	Ala 375	Pro	His	Ala	Met	Arg 380	His	Ile	Gln	Glu

His Tyr Gly Gly Thr Ala Thr Phe Tyr Leu Ser Gln Ala Ala Asp Gly 385 395

Ala Lys Val Leu Cys Leu 405

<210> 669

<211> 86

<212> PRT

<213> Homo sapiens

<400> 669

Pro Glu Pro Thr Val Val Met Ala Ala Arg Ala Leu Cys Met Leu Gly

Leu Val Leu Ala Leu Leu Ser Ser Ser Ser Ala Glu Glu Tyr Val Gly 25

Leu Ser Ala Asn Gln Cys Ala Val Pro Ala Lys Asp Arg Val Asp Cys

Gly Tyr Pro His Val Thr Pro Lys Glu Cys Asn Asn Arg Gly Cys Cys

Phe Asp Ser Arg Ile Pro Gly Val Pro Trp Cys Phe Lys Pro Leu Gln

Glu Ala Glu Cys Thr Phe

<210> 670

<211> 392

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<223> Xaa equals any of the naturally occurring L-amino acids

Gly Gly Gly Ala Arg Xaa Ser Pro Ala Thr Gln Pro Pro Pro Leu Leu

Pro Pro Ser Ala Thr Gly Pro Asp Ala Thr Val Gly Gly Pro Ala Pro

THE	PIO	35	Leu	PIO	PLO	ser	40	THE	Ald	ser	vai	45	Met	GIU	FIO
Glu	Asn 50	Lys	Tyr	Leu	Pro	Glu 55	Leu	Met	Ala	Glu	Lys 60	Asp	Ser	Leu	Asp
Pro 65	Ser	Phe	Thr	His	Ala 70	Met	Gln	Leu	Leu	Thr 75	Ala	Glu	Ile	Glu	B0
Ile	Gln	Lys	Gly	Asp 85	Ser	Lys	Lys	Asp	Asp 90	Glu	Glu	Asn	Tyr	Leu 95	Asp
Leu	Phe	Ser	His 100	Lys	Asn	Met	Lys	Leu 105	Lys	Glu	Arg	Val	Leu 110	Ile	Pro
Val	Lys	Gln 115	Tyr	Pro	Lys	Phe	Asn 120	Phe	Val	Gly	Lys	Ile 125	Leu	Gly	Pro
Gln	Gly 130	Asn	Thr	Ile	Lys	Arg 135	Leu	Gln	Glu	Glu	Thr 140	Gly	Ala	Lys	Ile
Ser 145	Val	Leu	Gly	Lys	Gly 150	Ser	Met	Arg	Asp	Lys 155	Ala	Lys	Glu	Glu	Glu 160
Leu	Arg	Lys	Gly	Gly 165	Asp	Pro	Lys	Tyr	Ala 170	His	Leu	Asn	Met	Asp 175	Leu
His	Val	Phe	Ile 180	Glu	Val	Phe	Gly	Pro 185	Pro	Суз	Glu	Ala	Туг 190	Ala	Leu
Met	Ala	His 195	Ala	Met	Glu	Glu	Val 200	Lys	Lys	Phe	Leu	Val 205	Pro	Asp	Met
Met	Asp 210	Asp	Ile	Cys	Gln	Glu 215	Gln	Phe	Leu	Glu	Leu 220	Ser	Tyr	Leu	Asn
Gly 225	Val	Pro	Glu	Pro	Ser 230	Arg	Gly	Arg	Gly	Val 235	Pro	Val	Arg	Gly	Arg 240
Gly	Ala	Ala	Pro	Pro 245	Pro	Pro	Pro	Val	Pro 250	Arg	Gly	Arg	Gly	Val 255	Gly
Pro	Pro	Arg	Gly 260	Ala	Leu	Val	Arg	Gly 265	Thr	Pro	Val	Arg	Gly 270	Ala	Ile
Thr	Arg	Gly 275	Ala	Thr	Val	Thr	Arg 280	Gly	Val	Pro	Pro	Pro 285	Pro	Thr	Val
Arg	Gly 290	Ala	Pro	Ala	Pro	Arg 295	Ala	Arg	Thr	Ala	Gly 300	Ile	Gln	Arg	Ile

Pro Leu Pro Pro Pro Ala Pro Glu Thr Tyr Glu Glu Tyr Gly Tyr 305 310 315 Asp Asp Thr Tyr Ala Glu Gln Ser Tyr Glu Gly Tyr Glu Gly Tyr Tyr 325 330 Ser Gln Ser Gln Gly Asp Ser Glu Tyr Tyr Asp Tyr Gly His Gly Glu 345 Val Gln Asp Ser Tyr Glu Ala Tyr Gly Gln Asp Asp Trp Asn Gly Thr 355 360 Arg Pro Ser Leu Lys Ala Pro Pro Ala Arg Pro Val Lys Gly Ala Tyr 380 375 Arg Glu His Pro Tyr Gly Arg Tyr 390 <210> 671 <211> 180 <212> PRT <213> Homo sapiens <400> 671 Arg Asn Met Ser Ser Phe Ser Arg Ala Pro Gln Gln Trp Ala Thr Phe Ala Arg Ile Trp Tyr Leu Leu Asp Gly Lys Met Gln Pro Pro Gly Lys 20 25 Leu Ala Ala Met Ala Ser Ile Arg Leu Gln Gly Leu His Lys Pro Val Tyr His Ala Leu Ser Asp Cys Gly Asp His Val Val Ile Met Asn Thr 55 Arg His Ile Ala Phe Ser Gly Asn Lys Trp Glu Gln Lys Val Tyr Ser Ser His Thr Gly Tyr Pro Gly Gly Phe Arg Gln Val Thr Ala Ala Gln 90 Leu His Leu Arg Asp Pro Val Ala Ile Val Lys Leu Ala Ile Tyr Gly 100 Met Leu Pro Lys Asn Leu His Arg Arg Thr Met Met Glu Arg Leu His 120

Leu Phe Pro Asp Glu Tyr Ile Pro Glu Asp Ile Leu Lys Asn Leu Val

130 135 140 Glu Glu Leu Pro Gln Pro Arg Lys Ile Pro Lys Arg Leu Asp Glu Tyr 150 155 Thr Gln Glu Glu Ile Asp Ala Phe Pro Arg Leu Trp Thr Pro Pro Glu 165 170 Asp Tyr Arg Leu 180 <210> 672 <211> 78 <212> PRT <213> Homo sapiens <400> 672 Glu Asn Tyr Gln Phe Thr Tyr Arg Arg Phe Phe Pro Asn Ser Arg Phe His Pro Arg Pro Phe Glu Glu Leu Gln Thr Leu Ser Leu Arg Lys 20 25 Glu Arg Gly Gln Pro Lys Ile Asn Ala Lys Phe Ala Tyr Thr Pro Ser His Ser Asp Val Leu Val Val Thr Tyr Tyr Gln Cys Gly Arg Glu Pro Lys Leu His Phe Arg Ser Lys Tyr Ser Leu Cys Arg Tyr Cys 70 <210> 673 <211> 139 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (113) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE

<223> Xaa equals any of the naturally occurring L-amino acids

<222> (132)

<400> 673

Pro Thr Arg Pro Pro Leu Cys Arg Gly Ala Ala Ser Arg Gly Leu Leu 10

Cys Lys Trp Ala Pro Trp Pro Ser Ala Pro Val Pro Ala Thr Arg Asp 25

Arg Ala Pro Arg Pro Ala Arg Gly Arg Arg Pro Gly Arg Leu Gly Ser 40

Thr Ser Ser Asn Ser Ser Cys Ser Ser Thr Glu Cys Pro Gly Glu Ala

Ile Pro His Pro Pro Gly Leu Pro Lys Ala Asp Pro Gly His Trp Trp 70 75

Ala Ser Phe Phe Phe Gly Lys Ser Thr Leu Pro Phe Met Ala Thr Val

Leu Glu Ser Ala Glu His Ser Glu Pro Pro Gln Ala Ser Ser Ser Met 105

Xaa Ala Cys Gly Leu Ala Arg Glu Ala Pro Arg Lys Gln Pro Gly Gly 120

Gln Ser Ser Xaa Ala Ser Ala Gly Pro Pro Ser 130 135

<210> 674

<211> 279

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (7)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (58)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (193)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 674

Glu 1	Arg	Ala	His	Ser 5	Leu	Xaa	His	Gly	Val 10	Asp	Gly	Glu	Pro	Cys 15	Pro
Glu	Asp	Tyr	Lys 20	Tyr	Ile	Ser	Glu	Asn 25	Cys	Glu	Thr	Ser	Thr 30	Met	Asn
Ile	Asp	Arg 35	Asn	Ile	Thr	His	Leu 40	Gln	His	Cys	Thr	Phe 45	Val	Asp	Asp
Cys	Ser 50	Ser	Ser	Asn	Суѕ	Leu 55	Cys	Gly	Xaa	Phe	Ser 60	Ile	Arg	Cys	Trp
Tyr 65	Asp	Lys	Asp	Gly	Arg 70	Leu	Leu	Gln	Glu	Phe 75	Asn	Lys	Ile	Glu	Pro 80
Pro	Leu	Ile	Phe	Glu 85	Cys	Asn	Gln	Ala	90 Суз	Ser	Cys	Trp	Arg	Asn 95	Суѕ
Lys	Asn	Arg	Val 100	Val	Gln	Ser	Gly	11e 105	Lys	Val	Arg	Leu	Gln 110	Leu	Tyr
Arg	Thr	Ala 115	Lys	Met	Gly	Trp	Gly 120	Val	Arg	Ala	Leu	Gln 125	Thr	Ile	Pro
Gln	Gly 130	Thr	Phe	Ile	Cys	Glu 135	Tyr	Val	Gly	Glu	Leu 140	Ile	Ser	Asp	Ala
Glu 145	Ala	Asp	Val	Arg	Glu 150	Asp	Asp	Ser	Tyr	Leu 155	Phe ·	Asp	Leu	Asp	Asn 160
Lys	Asp	Gly	Glu	Val 165	Tyr	Cys	Ile	Asp	Ala 170	Arg	Tyr	Tyr	Gly	Asn 175	Ile
Ser	Arg	Phe	Ile 180	Asn	His	Leu	Cys	Asp 185	Pro	Asn	Ile	Ile	Pro 190	Val	Arg
Xaa	Phe	Met 195	Leu	His	Gln	Asp	Leu 200	Arg	Phe	Pro	Arg	11e 205	Ala	Phe	Phe
Ser	Ser 210	Arg	Asp	Ile	Arg	Thr 215	Gly	Glu	Glu	Leu	Gly 220	Phe	Asp	Tyr	Gly
Asp 225	Arg	Phe	Trp	Asp	Ile 230	Lys	Ser	Lys	Tyr	Phe 235	Thr	Суз	Gln	Cys	Gly 240
Ser	Glu	Lys	Cys	Lys 245	His	Ser	Ala	Glu	Ala 250	Ile	Ala	Leu	Glu	Gln 255	Ser
Arg	Leu	Ala	Arg 260	Leu	Asp	Pro	His	Pro 265	Glu	Leu	Leu	Pro	Glu 270	Leu	Gly

Ser Leu Pro Pro Val Asn Thr 275

<210> 675 <211> 405 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (393) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (394) <223> Xaa equals any of the naturally occurring L-amino acids <400> 675 Arg Asn Thr Leu Gly Arg Gly Thr Thr Ile Thr Leu Val Leu Lys Glu 10 Glu Ala Ser Asp Tyr Leu Glu Leu Asp Thr Ile Lys Asn Leu Val Lys 20 25 Lys Tyr Ser Gln Phe Ile Asn Phe Pro Ile Tyr Val Trp Ser Ser Lys Thr Glu Thr Val Glu Glu Pro Met Glu Glu Glu Glu Ala Ala Lys Glu 55 Glu Lys Glu Glu Ser Asp Asp Glu Ala Ala Val Glu Glu Glu Glu Glu 70 75 Glu Lys Lys Pro Lys Thr Lys Lys Val Glu Lys Thr Val Trp Asp Trp Glu Leu Met Asn Asp Ile Lys Pro Ile Trp Gln Arg Pro Ser Lys Glu 105 Val Glu Glu Asp Glu Tyr Lys Ala Phe Tyr Lys Ser Phe Ser Lys Glu 115 120 Ser Asp Asp Pro Met Ala Tyr Ile His Phe Thr Ala Glu Gly Glu Val 135

Thr Phe Lys Ser Ile Leu Phe Val Pro Thr Ser Ala Pro Arg Gly Leu

155

Phe	Asp	Glu	Tyr	Gly 165	Ser	Lys	Lys	Ser	Asp 170	Tyr	Ile	Lys	Leu	Tyr 175	Val
Arg	Arg	Val	Phe 180	Ile	Thr	Asp	Asp	Phe 185	His	Asp	Met	Met	Pro 190	Lys	Tyr
Leu	Asn	Phe 195	Val	Lys	Gly	Val	Val 200	Asp	Ser	Asp	Asp	Leu 205	Pro	Leu	Asn
Val	Ser 210	Arg	Glu	Thr	Leu	Gln 215	Gln	His	Lys	Leu	Leu 220	Lys	Val	Ile	Arg
Lys 225	Lys	Leu	Val	Arg	Lys 230	Thr	Leu	Asp	Met	11e 235	Lys	Lys	Ile	Ala	Asp 240
Asp	Lys	Tyr	Asn	Asp 245	Thr	Phe	Trp	Lys	Glu 250	Phe	Gly	Thr	Asn	Ile 255	Lys
Leu	Gly	Val	11e 260	Glu	Asp	His	Ser	Asn 265	Arg	Thr	Arg	Leu	Ala 270	Lys	Leu
Leu	Arg	Phe 275	Gln	Ser	Ser	His	His 280	Pro	Thr	Asp	Ile	Thr 285	Ser	Leu	Asp
Gln	Tyr 290	Val	Glu	Arg	Met	Lys 295	Glu	Lys	Gln	Asp	Lys 300	Ile	Tyr	Phe	Met
305	_				Lys 310					315					320
		-	·	325	Tyr				330					335	_
	-	•	340		Ala			345		·	•	-	350		
		355			Gly		360					365			
	370				Val	375					380				
385					190	Lys	Gly	Xaa	Xaa	195	Trp	Glu	Ile	Leu	Pro 400
Ile	Cys	Gly	Lys	Tyr 405											

646

<211> 465 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (5) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (6) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (16) <223> Xaa equals any of the naturally occurring L-amino acids <400> 676 Asn Asp Ser Leu Xaa Xaa Lys Ala Gly Thr Pro Ala Gly Asn Arg Xaa 5 Gly Ile Pro Gly Ser Thr His Ala Ser Ala Ala Ala Pro Phe Ala Ala Ala Leu Ala Arg Asp Pro Asn Pro Ala Ser Pro Leu Pro Glu His Arg Pro Arg Leu His Arg Gly Pro Gly Pro Pro Ala Arg Leu Ala Ala Ala Met Ala Asp Pro Lys Tyr Ala Asp Leu Pro Gly Ile Ala Arg Asn Glu Pro Asp Val Tyr Glu Thr Ser Asp Leu Pro Glu Asp Asp Gln Ala Glu 85 90 Phe Asp Ala Glu Glu Leu Thr Ser Thr Ser Val Glu His Ile Ile Val 100 Asn Pro Asn Ala Ala Tyr Asp Lys Phe Lys Asp Lys Arg Val Gly Thr 120 Lys Gly Leu Asp Phe Ser Asp Arg Ile Gly Lys Thr Lys Arg Thr Gly Tyr Glu Ser Gly Glu Tyr Glu Met Leu Gly Glu Gly Leu Gly Val Lys 150 145

Glu Thr Pro Gln Gln Lys Tyr Gln Arg Leu Leu His Glu Val Gln Glu

				165					170					175	
Leu	Thr	Thr	Glu 180	Val	Glu	Lys	Ile	Lys 185	Thr	Thr	Val	Lys	Glu 190	Ser	Ala
Thr	Glu	Glu 195	Lys	Leu	Thr	Pro	Val 200	Leu	Leu	Ala	Lys	Gln 205	Leu	Ala	Ala
Leu	Lys 210		Gln	Leu	Val	Ala 215	Ser	His	Leu	Glu	Lys 220	Leu	Leu	Gly	Pro
Asp 225	Ala	Ala	Ile	Asn	Leu 230	Thr	Asp	Pro	Asp	Gly 235	Ala	Leu	Ala	Lys	Arg 240
Leu	Leu	Leu	Gln	Leu 245	Glu ,	Ala	Thr	Lys	Asn 250	Ser	Lys	Gly	Gly	Ser 255	Gly
Gly	Lys	Thr	Thr 260	Gly	Thr	Pro	Pro	Asp 265	Ser	Ser	Leu	Val	Thr 270	Tyr	Glu
Leu	His	Ser 275	Arg	Pro	Glu	Gln	Asp 280	Lys	Phe	Ser	Gln	Ala 285	Ala	Lys	Val
Ala	Glu 290	Leu	Glu	Lys	Arg	Leu 295	Thr	Glu	Leu	Glu	Thr 300	Ala	Val	Arg	Cys
Asp 305	Gln	Asp	Ala	Gln	Asn 310	Pro	Leu	Ser	Ala	Gly 315	Leu	Gln	Gly	Ala	Cys 320
Leu	Met	Glu	Thr	Val 325	Glu	Leu	Leu	Gln	Ala 330	Lys	Val	Ser	Ala	Leu 335	Asp
Leu	Ala	Val	Leu 340	Asp	Gln	Val	Glu	Ala 345	Arg	Leu	Gln	Ser	Val 350	Leu	Gly
Lys	Val	Asn 355	Glu	Ile	Ala	Lys	His 360	Lys	Ala	Ser	Val	Glu 365	Asp	Ala	Asp
Thr	Gln 370	Ser	Lys	Val	His	Gln 375	Leu	Tyr	Glu	Thr	ile 380	Gln	Arg	Trp	Ser
Pro 385	Ile	Ala	Ser	Thr	Leu 390	Pro	Glu	Leu	Val	Gln 395	Arg	Leu	Val	Thr	11e 400
Lys	Gln	Leu	His	Glu 405	Gln	Ala	Met	Gln	Phe 410	Gly	Gln	Leu	Leu	Thr 415	His
Leu	Asp	Thr	Thr 420	Gln	Gln	Met	Ile	Ala 425	Asn	Ser	Leu	Lys	Asp 430	Asn	Thr
Thr	Leu	Leu	Thr	Gln	Val	Gln	Thr	Thr	Met	Arg	Glu	Asn	Leu	Ala	Thr

648

435 440 445

Val Glu Gly Asn Phe Ala Ser Ile Asp Glu Arg Met Lys Lys Leu Gly
450 460

Lys 465

<210> 677

<211> 48

<212> PRT

<213> Homo sapiens

<400> 677

Ser Ser Phe Leu Asn Ser Asp Leu Gly Leu Ser Leu Ala Arg Asn Leu $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$

Ala Phe Ser Phe Thr Thr Lys Glu Arg Asp Gln Lys Pro Leu Ile Phe 20 25 30

Asn Phe His Lys Met Leu Glu Val Tyr Ile Tyr Ile Tyr Ile Phe Leu 35 40 45

<210> 678

<211> 940

<212> PRT

<213> Homo sapiens

<400> 678

Val Leu Gly Glu Gly Ile Ser Phe Leu Leu Ser Pro Pro Leu Pro Thr
1 5 10 15

Pro Ser Ile Asn Ile Ile Leu Leu Lys Ile Leu Arg Cys Gln Ala Ala 20 25 30

Lys Val Glu Ser Ala Ile Ala Glu Gly Gly Ala Ser Arg Phe Ser Ala 35 40 45

Ser Ser Gly Gly Gly Ser Arg Gly Ala Pro Gln His Tyr Pro Lys
50 60

Thr Ala Gly Asn Ser Glu Phe Leu Gly Lys Thr Pro Gly Gln Asn Ala 65 70 75 80

Gln	Lys	Trp	Ile	Pro 85	Ala	Arg	Ser	Thr	Arg 90	Arg	Asp	Asp	Asn	Ser 95	Ala
Ala	Asn	Asn	Ser 100	Ala	Asn	Glu	Lys	Glu 105	Arg	His	Asp	Ala	Ile 110	Phe	Arg
Lys	Val	Arg 115	Gly	Ile	Leu	Asn	Lys 120	Leu	Thr	Pro	Glu	Lys 125	Phe	Asp	Lys
Leu	Cys 130	Leu	Glu	Leu	Leu	Asn 135	Val	Gly	Val	Glu	Ser 140	Lys	Leu	Ile	Leu
Lys 145	Gly	Val	Ile	Leu	Leu 150	Ile	Val	Asp	Lys	Ala 155	Leu	Glu	Glu	Pro	Lys 160
Tyr	Ser	Ser	Leu	Tyr 165	Ala	Gln	Leu	Суз	Leu 170	Arg	Leu	Ala	Glu	Asp 175	Ala
Pro	Asn	Phe	Asp 180	Gly	Pro	Ala	Ala	Glu 185	Gly	Gln	Pro	Gly	Gln 190	Lys	Gln
Ser	Thr	Thr 195	Phe _.	Arg	Arg	Leu	Leu 200	Ile	Ser	Lys	Leu	Gln 205	Asp	Glu	Phe
Glu	Asn 210	Arg	Thr	Arg	Asn	Val 215	Asp	Val	Tyr	Asp	Lys 220	Arg	Glu	Asn	Pro
Leu 225	Leu	Pro	Glu	Glu	Glu 230	Glu	Gln	Arg	Ala	Ile 235	Ala	Lys	Ile	Lys	Met 240
Leu	Gly	Asn	Ile	Lys 245	Phe	Ile	Gly	Glu	Leu 250	Gly	Lys	Leu	Asp	Leu 255	Ile
His	Glu	Ser	Ile 260	Leu	His	Lys	Cys	11e 265	Lys	Thr	Leu	Leu	Glu 270	Lys	Lys
Lys	Arg	Val 275	Gln	Leu	Lys	Asp	Met 280	Gly	Glu	Asp	Leu	Glu 285	Cys	Leu	Суз
Gln	Ile 290	Met	Arg	Thr	Val	Gly 295	Pro	Arg	Leu	Asp	His 300	Glu	Arg	Ala	Lys
Ser 305	Leu	Met	Asp	Gln	Tyr 310	Phe	Ala	Arg	Met	Cys 315	Ser	Leu	Met	Leu	Ser 320
Lys	Glu	Leu	Pro	Ala 325	Arg	Ile	Arg	Phe	Leu 330	Leu	Gln	Asp	Thr	Val 335	Glu
Leu	Arg	Glu	His 340	His	Trp	Val	Pro	Arg 345	Lys	Ala	Phe	Leu	Asp 350	Asn	Gly

PFO	rys	355	116	AST	GIN	iie	360	GIN	ASP	Ala	Val	365	мзр	Leu	GIY
Val	Phe 370	Ile	Pro	Ala	Pro	Met 375	Ala	Gln	Gly	Met	Arg 380	Ser	Asp	Phe	Phe
Leu 385	Glu	Gly	Pro	Phe	Met 390	Pro	Pro	Arg	Met	Lys 395	Met	Asp	Arg	Asp	Pro 400
Leu	Gly	Gly	Leu	Ala 405	Asp	Met	Phe	Gly	Gln 410	Met	Pro	Gly	Ser	Gly 415	Ile
Gly	Thr	Gly	Pro 420	Gly	Val	Ile	Gln	Asp 425	Arg	Phe	Ser	Pro	Thr 430	Met	Gly
Arg	His	Arg 435	Ser	Asn	Gln	Leu	Phe 440	Asn	Gly	His	Gly	Gly 445	His	Ile	Met
Pro	Pro 450	Thr	Gln	Ser	Gln	Phe 455	Gly	Glu	Met	Gly	Gly 460	Lys	Phe	Met	Lys
Ser 465	Gln	Gly	Leu	Ser	Gln 470	Leu	Tyr	His	Asn	Gln 475	Ser	Gln	Gly	Leu	Leu 480
Ser	Gln	Leu	Gln	Gly 485	Gln	Ser	Lys	Asp	Мѐт 490	Pro	Pro	Arg	Phe	Ser 495	Lys
Lys	Gly	Gln	Leu 500	Asn	Ala	Asp	Glu	Ile 505	Ser	Leu	Arg	Pro	Ala 510	Gln	Ser
Phe	Leu	Met 515	Asn	Lys	Asn	Gln	Val 520	Pro	Lys	Leu	Gln	Pro 525	Gln	Ile	Thr
Met	11e 530	Pro	Pro	Ser	Ala	Gln 535	Pro	Pro	Arg	Thr	Gln 540	Thr	Pro	Pro	Leu
545				Gln	550	_		_		555					560
Glu	Lys	Pro	Ala	Lys 565	Thr'	Ser	Lys	Lys	Pro 570	Pro	Pro	Ser	Lys	Glu 575	Glu
Leu	Leu	Lys	Leu 580	Thr	Glu	Thr	Val	Val 585	Thr	Glu	Tyr	Leu	Asn 590	Ser	Gly
Asn	Ala	Asn 595	Glu	Ala	Val	Asn	Gly 600	Val	Arg	Glu	Met	Arg 605	Ala	Pro	Lys
His	Phe 610	Leu	Pro	Glu		Leu 615	Ser	Lys	Val	Ile	Ile 620	Leu	Ser	Leu	Asp

PCT/US00/05881 WO 00/55173

65 l

625	261	ASP	GIU	ASP	630	GIU	ràs	MIG	261	635	rea	116	261	Dea	640
Lys	Gln	Glu	Gly	Ile 645	Ala	Thr	Ser	Asp	Asn 650	Phe	Met	Gln	Ala	Phe 655	Leu
Asn	Val	Leu	Asp 660	Gln	Cys	Pro	Lys	Leu 665	Glu	Val	Asp	Ile	Pro 670	Leu	Val
Lys	Ser	Tyr 675	Leu	Ala	Gln	Phe	Ala 680	Ala	Arg	Ala	Ile	Ile 685	Ser	Glu	Leu
Val	Ser 690	Ile	Ser	Glu	Leu	Ala 695	Gln	Pro	Leu	Glu	Ser 700	Gly	Thr	His	Phe
Pro 705	Leu	Phe	Leu	Leu	Cys 710	Leu	Gln	Gln	Leu	Ala 715	Lys	Leu	Gln	Asp	Arg 720
				725	Leu				730					735	_
			740		Asp			745					750		
	-	755			Ser		760					765			
	770		-		Ile	775		-			780				
785	_			_	790				_	795					800
				805	Met				810		-			815	
			820		Asp			825					830		
		835			Glu	-	840					845	-		
	850	_			His	855					860				
865					His 870	_				875			_		880
Leu	Leu	Arg	Phe	Phe 885	Val	His	Phe	Tyr	Asp 890	Met	Glu	Ile	Ile	Glu 895	Glu

Glu Ala Phe Leu Ala Trp Lys Glu Asp Ile Thr Gln Glu Phe Pro Gly 900 905 910

Lys Gly Lys Ala Leu Phe Gln Val Asn Gln Trp Leu Thr Trp Leu Glu 915 920 925

Thr Ala Glu Glu Glu Glu Ser Glu Glu Glu Ala Asp 930 935 940

<210> 679

<211> 212

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (7)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (160)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (172)

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<400> 679

Ser Trp Lys Glu Glu Glu Xaa Lys Pro His Leu Gln Gly Lys Pro Gly
1 5 10 15

Arg Pro Leu Ser Pro Ala Asn Val Pro Ala Leu Pro Gly Glu Thr Val 20 25 30

Thr Ser Pro Val Arg Leu His Pro Asp Tyr Leu Ser Pro Glu Glu Ile 35 40 45

Gln Arg Gln Leu Gln Asp Ile Glu Arg Arg Leu Asp Ala Leu Glu Leu 50 60

Arg Gly Val Glu Leu Glu Lys Arg Leu Arg Ala Ala Glu Gly Asp Asp 65 70 75 80

Ala Glu Asp Ser Leu Met Val Asp Trp Phe Trp Leu Ile His Glu Lys 85 90 95

Gln Leu Leu Arg Gln Glu Ser Glu Leu Met Tyr Lys Ser Lys Ala

653

105

100

110

Gln Arg Leu Glu Glu Gln Gln Leu Asp Ile Glu Gly Glu Leu Arg Arg 120 Leu Met Ala Lys Pro Glu Ala Leu Lys Ser Leu Gln Glu Arg Arg 135 Glu Gln Glu Leu Leu Glu Gln Tyr Val Ser Thr Val Asn Asp Arg Xaa Asp Ile Val Asp Ser Leu Asp Glu Asp Arg Leu Xaa Glu Gln Glu Glu 165 170 Asp Gln Met Leu Arg Asp Met Ile Glu Lys Leu Gly Leu Gln Arg Lys Lys Ser Lys Phe Arg Leu Ser Lys Ile Trp Ser Pro Lys Ser Lys Ser 200 Ser Pro Ser Gln 210 <210> 680 <211> 412 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (172) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (404) <223> Xaa equals any of the naturally occurring L-amino acids <400> 680 Val Ala Val Glu Leu Gly Ser Leu Arg Gly Gly Thr Met Ala Ser Glu Lys Pro Leu Ala Ala Val Thr Cys Thr Ala Pro Val Asn Ile Ala Val Ile Lys Tyr Trp Gly Lys Arg Asp Glu Glu Leu Val Leu Pro Ile Asn 40 Ser Ser Leu Ser Val Thr Leu His Gln Asp Gln Leu Lys Thr Thr Thr

	50					55					60				
Thr 65	Ala	Val	Ile	Ser	Lys 70	Asp	Phe	Thr	Glu	Asp 75	Arg	Ile	Trp	Leu	Asn 80
Gly	Arg	Glu	Glu	Asp 85	Val	Gly	Gln	Pro	Arg 90	Leu	Gln	Ala	Cys	Leu 95	Arg
Glu	Ile	Arg	Cys 100	Leu	Ala	Arg	Lys	Arg 105	Arg	Asn	Ser	Arg	Asp 110	Gly	Asp
Pro	Leu	Pro 115	Ser	Ser	Leu	Ser	Cys 120	Lys	Val	His	Val	Ala 125	Ser	Val	Asn
Asn	Phe 130	Pro	Thr	Ala	Ala	Gly 135	Leu	Ala	Ser	Ser	Ala 140	Ala	Gly	Tyr	Ala
Cys 145	Leu	Ala	Tyr	Thr	Leu 150	Ala	Arg	Val	туг	Gly 155	Val	Glu	Ser	Asp	Leu 160
Ser	Glu	Val	Ala	Arg 165	Arg	Gly	Ser	Gly	Ser 170	Ala	Xaa	Arg	Ser	Leu 175	Tyr
Gly	Gly	Phe	Val 180	Glu	Trp	Gln	Met	Gly 185	Glu	Gln	Ala	Asp	Gly 190	Lys	Asp
Ser	Ile	Ala 195	Arg	Gln	Val	Ala	Pro 200	Glu	Ser	His	Trp	Pro 205	Glu	Leu	Arg
Val	Leu 210	Ile	Leu	Val	Val	Ser 215	Ala	Glu	Lys	Lys	Leu 220	Thr	Gly	Ser	Thr
Val 225	Gly	Met	Arg	Ala	Ser 230	Val	Glu	Thr	Ser	Pro 235	Leu	Leu	Arg	Phe	Arg 240
Ala	Glu	Ser	Val	Val 245	Pro	Ala	Arg	Met	Ala 250	Glu	Met	Ala	Arg	Суз 255	Ile
Arg	Glu	Arg	Asp 260	Phe	Pro	Ser	Phe	Ala 265	Gln	Leu	Thr	Met	Lys 270	Asp	Ser
Asn	Gln	Phe 275	His	Ala	Thr	Суѕ	Leu 280	Asp	Thr	Phe	Pro	Pro 285	Ile	Ser	Tyr
Leu	Asn 290	Ala	Ile	Ser	Trp	Arg 295	Ile	Ile	His	Leu	Val 300	His	Arg	Phe	Asn
Ala 305	His	His	Gly	Asp	Thr 310	Lys	Val	Ala	туг	Thr 315	Phe	Asp	Ala	Gly	Pro 320
Asn	Ala	Val	Ile	Phe	Thr	Leu	Asp	Asp	Thr	Val	Ala	Glu	Phe	Val	Ala

655

325 330 335 Ala Val Trp His Gly Phe Pro Pro Gly Ser Asn Gly Asp Thr Phe Leu 340 345 Lys Gly Leu Gln Val Arg Pro Ala Pro Leu Ser Ala Glu Leu Gln Ala 360 355 Ala Leu Ala Met Glu Pro Thr Pro Gly Gly Val Lys Tyr Ile Ile Val 375 Thr Gln Val Gly Pro Gly Pro Gln Ile Leu Asp Asp Pro Cys Ala His 385 390 395 Leu Leu Gly Xaa Asp Gly Leu Pro Lys Pro Ala Ala 405 <210> 681 <211> 61 <212> PRT <213> Homo sapiens <400> 681 Lys Lys Thr Arg His Leu Ser Lys Ile Leu Cys Gly Lys Met Thr Val 10 . Asn Lys Met Arg Val Ser Gly Pro Phe Val Leu Leu Ser Phe Phe Asp 25 Tyr Lys Phe Leu Leu Thr His Thr Ile Met Ser Ala Asn Pro Leu Leu 35 40 Pro Arg Glu Arg Asn Cys Ala Pro Ser Val Leu Leu Pro 50 55 <210> 682 <211> 243 <212> PRT <213> Homo sapiens <400> 682 Ser Ala Pro Pro Pro Pro Arg Arg Lys Thr Ala Pro Pro Ala His Arg 10

Gln Arg Pro Pro Pro Gln Ser Pro Thr Ala Thr Gly Leu Gly Pro Ala

656

Ala	Arg	Ser	Cys	Leu	Pro	Gln	Pro	Pro	Ser	Arg	Gly	Pro	Gln	Pro	Pro
		35					40					45			

- Pro Thr Leu Pro His Gly Pro Gly Ala Met Ser Glu Leu Glu Gln Leu 50 55 60
- Arg Gln Glu Ala Glu Gln Leu Arg Asn Gln Ile Arg Asp Ala Arg Lys
 65 70 75 80
- Ala Cys Gly Asp Ser Thr Leu Thr Gln Ile Thr Ala Gly Leu Asp Pro
 85 90 95
- Val Gly Arg Ile Gln Met Arg Thr Arg Arg Thr Leu Arg Gly His Leu 100 105 110
- Ala Lys Ile Tyr Ala Met His Trp Gly Thr Asp Ser Arg Leu Leu Val 115 120 125
- Ser Ala Ser Gln Asp Gly Lys Leu Ile Ile Trp Asp Ser Tyr Thr Thr 130 135 140
- Asn Lys Val His Ala Ile Pro Leu Arg Ser Ser Trp Val Met Thr Cys 145 150 155 160
- Ala Tyr Ala Pro Ser Gly Asn Phe Val Ala Cys Gly Gly Leu Asp Asn 165 170 175
- Ile Cys Ser Ile Tyr Ser Leu Lys Thr Arg Glu Ala Thr Ser Gly Ser 180 185 190
- Ala Gly Ser Cys Leu Ala Thr Leu Gly Thr Cys Arg Val Ala Ala Ser 195 200 205
- Trp Met Thr Thr Lys Ser Ser Pro Ala Leu Gly Ile Pro Pro Val Pro 210 215 220
- Cys Gly Thr Leu Arg Gln Ala Ser Arg Gln Trp Val Leu Leu Asp Thr 225 230 235 240

Val Gly Met

<220>

<221> SITE

<210> 683

<211> 146

<212> PRT

<213> Homo sapiens

657

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25

Trp His Arg Leu Pro Ser Thr Ser Gln Leu His Leu Cys Pro Ala Glu

. 40

Gly	Glu 50	Ala	Pro	Ser	Ala	Gly 55	Glu	Ala	Ala	Pro	Arg 60	Ala	Pro	Thr	Gly
Ser 65	Glu	Pro	Lys	Pro	Gly 70	Ala	Leu	Pro	Trp	Gly 75	Pro	Arg	Ala	Pro	Asp 80
Ser	Glu	Gly	Gly	Gly 85.	Gly	Ala	Gly	Ala	Ala 90	Asp	Pro	Ala	Ala	Asn 95	Ala
Gly	His	Gly	Ala 100	Ser	Ser	Glu	Ala	Glu 105	Cys	Gly	Cys	Gln	Arg 110	Thr	Leu
Arg		Met 115	Pro	Ser	Thr	Pro	Gly 120	Pro	Gly	Ala	Ala	Ala 125	Val	Arg	Ala
Leu	Gly 130	Gln	Leu	Phe	His	11e 135	Ala	Cys	Phe	Thr	Cys 140	His	Gln	Cys	Ala
Gln 145	Gln	Leu	Gln	Gly	Gln 150	Gln	Phe	Tyr	Ser	Leu 155	Glu	Gly	Ala	Pro	Туг 160
Суз	Glu	Gly	Cys	Tyr 165	Thr	Asp	Thr	Leu	Glu 170	Lys	Cys	Asn	Thr	Cys 175	Gly
Glu	Pro	Ile	Thr 180	Asp	Arg	Met	Leu	Arg 185	Ala	Thr	Gly	Lys	Ala 190	Tyr	His
Pro	His	Cys 195	Phe	Thr	Cys	Val	Val 200	Cys	Ala	Arg	Pro	Leu 205	Glu	Gly	Thr
Ser	Phe 210	Ile	Val	Asp	Gln	Ala 215	Asn	Arg	Pro	His	Cys 220	Val	Pro	Asp	туг
His 225	Lys	Gln	Tyr	Ala	Pro 230	Arg	Cys	Ser	Val	Cys 235	Ser	Glu	Pro	Ile	Met 240
Pro	Glu	Pro	Gly	Arg 245	Asp	Glu	Thr	Val	Arg 250	Val	Val	Ala	Leu	Asp 255	Lys
Asn	Phe	His	Met 260	ГÀЗ	Суз	Tyr	Lys	Cys 265	Glu	Asp	Cys	Gly	Lys 270	Pro	Leu
Ser	Ile	Glu 275	Ala	Asp	Asp	Asn	Gly 280	Cys	Phe	Pro	Leu	Asp 285	Gly	His	Val
Leu	Cys 290	Arg	Lys	Сув	His	Thr 295	Ala	Arg	Ala	Gln	Thr 300				

659

<211> 130

<212> PRT

<213> Homo sapiens

<220>

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<222> (61)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 685

Ile Arg His Glu Asp Cys Pro Thr Pro Ser Gln Cys Val Val Ala Arg

Thr Leu Gly Lys Gln Gln Thr Val Met Ala Ile Ala Thr Lys Ile Ala 20 25 30

Leu Gln Met Asn Cys Lys Met Gly Gly Glu Leu Trp Arg Val Asp Ile 35 40 45

Pro Leu Lys Leu Val Met Ile Val Gly Ile Asp Cys Xaa His Asp Met 50 55 60

Thr Ala Gly Arg Arg Ser Ile Ala Gly Phe Val Ala Ser Ile Asn Glu 65 70 75 80

Gly Met Thr Arg Trp Phe Ser Arg Cys Ile Phe Gln Asp Arg Gly Gln 85 90 95

Glu Leu Val Asp Gly Leu Lys Val Cys Leu Gln Ala Ala Leu Arg Ala 100 105 110

Trp Asn Ser Cys Asn Glu Tyr Met Pro Ser Arg Ile Ile Val Tyr Arg 115 120 125

Val Ala 130

<210> 686 <211> 207

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (84)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 686

Ile Tyr Gln Val Tyr Asn Ala Leu Gln Glu Lys Val Gln Ala Val Cys

660

1				5					10					15	
Ala	Asp	Val	Glu 20	Lys	Ser	Glu	Arg	Val 25	Val	Glu	Ser	Cys	Gln 30	Ala	Glu
Val	Asn	Lys 35	Leu	Arg	Arg	Gln	Ile 40	Thr	Gln	Arg	Lys	Asn 45	Glu	Lys	Glu
Gln	Glu 50	Arg	Arg	Leu	Gln	Gln 55	Ala	Val	Leu	Ser	Arg 60	Gln	Met	Pro	Ser
Glu 65	Ser	Leu	Asp	Pro	Ala 70	Phe	Ser	Pro	Arg	Met 75	Pro	Ser	Ser	Gly	Phe 80
Ala	Ala	Glu	Xaa	Arg 85	Ser	Thr	Leu	Gly	Asp 90	Ala	Glu	Ala	Ser	Asp 95	Pro
Pro	Pro	Pro	Tyr 100	Ser	Asp	Phe	His	Pro 105	Asn	Asn	Gln	Glu	Ser 110	Thr	Leu
Ser	His	Ser 115	Arg	Met	Glu	Arg	Ser 120	Val	Phe	Met	Pro	Arg 125	Pro	Gln	Ala
Val	Gly 130	Ser	Ser	Asn	Tyr	Ala 135	Ser	Thr	Ser	Ala	Gly 140	Leu	Lys	Tyr	Pro
Gly 145	Ser	Gly	Ala	Asp	Leu 150	Pro	Pro	Pro	Gln	Arg 155	Ala	Ala	Gly	Asp	Ser 160
Gly	Glu	Asp	Ser	Asp 165	Asp	Ser	Asp	Tyr	Glu 170	Asn	Leu	Ile	Asp	Pro 175	Thr
Glu	Pro	Ser	Asn 180	Ser	Glu	Tyr	Ser	His 185	Ser	Lys	Asp	Ser	Arg 190	Pro	Met
Ala	His	Pro 195	Asp	Glu	Asp	Pro	Arg 200	Asn	Thr	Gln	Thr	Ser 205		Ile	
<211		1													
<212> PRT <213> Homo sapiens															
•															
<400 Ala	> 68 Arg		Gly	Glu	Glu	Gly	Val	Val	Thr	Arg	Trp	Arg	His	Arg	Leu

Gly Gln Gly Ala Cys Pro Trp Asp Arg Ser Arg Pro Met Glu Pro Pro 20 25 30

661

Gly Arg Ser Ser Arg Ser Thr Ala Ser His Thr Leu His Gln Tyr Cys

Cys Pro Thr Gln Val Leu Asp Ser Met Lys Leu Thr Pro Ser Gly Arg

Leu Ala Glu Ser Arg Glu Glu Glu Glu Glu Glu Thr Glu Glu Glu

Glu Glu Glu Asp Ala His Gln Phe Cys Cys Pro Ala Ser Glu Cys Ser 90

Ser Pro Ser Ser Arg 100

<210> 688

<211> 62

<212> PRT

<213> Homo sapiens

Glu Arg Asn Ala Asp Pro Pro Asp Val Ser Leu Gly Lys Ala Val Asn 1 5

Gln Leu Ile Phe Ile Glu Asp Leu Leu Cys Pro Leu His Arg Val Ala

Ser Val Arg Glu Ser Trp Phe Phe Pro Arg Asn Thr Asp Phe Leu Ser 40

Gly Arg Leu His Val Phe Ile Tyr Phe His His Ser Arg Phe 50 55

<210> 689

<211> 549

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (1)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (7)

<22	3> X	aa e	qual	s an	y of	the	nat	ural	ly o	ccur	ring	L-a	mino	aci	ds
	0> 6									_					
Xaa 1	Arg	Trp	Ala	Cys 5	Gly	Xaa	Leu	Leu	Leu 10	Leu	Val	Arg	Gly	G1n 15	Gly
Gln	Asp	Ser	Ala 20	Ser	Pro	Ile	Arg	Thr 25	Thr	His	Thr	Gly	Gln 30	Val	Leu
Gly	Ser	Leu 35	Val	His	Val	Lys	Gly 40	Ala	Asn	Ala	Gly	Val 45	Gln	Thr	Phe
Leu	Gly 50	Ile	Pro	Phe	Ala	Lys 55	Pro	Pro	Leu	Gly	Pro 60	Leu	Arg	Phe	Ala
Pro 65	Pro	Glu	Pro	Pro	Glu 70	Ser	Trp	Ser	Gly	Val 75	Arg	Asp	Gly	Thr	Thr 80
His	Pro	Ala	Met	Cys 85	Leu	Gln	Asp	Leu	Thr 90	Ala	Val	Glu	Ser	Glu 95	Phe
Leu	Ser	Gln	Phe 100	Asn	Met	Thr	Phe	Pro 105	Ser	Asp	Ser	Met	Ser 110	Glu	Asp
Cys	Leu	Tyr 115	Leu	Ser	Ile	Tyr	Thr 120	Pro	Ala	His	Ser	His 125	Glu	Gly	Ser
Asn	Leu 130	Pro	Val	Met	Val	Trp 135	Ile	His	Gly	Gly	Ala 140	Leu	Val	Phe	Gly
Met 145	Ala	Ser	Leu	Tyr	Asp 150	Gly	Ser	Met	Leu	Ala 155	Ala	Leu	Glu	Asn	Val 160
Val	Val	Val	Ile	Ile 165	Gln	Tyr	Arg	Leu	Gly 170	Val	Leu	Gly	Phe	Phe 175	Ser
Thr	Gly	Asp	Lys 180	His	Ala	Thr	Gly	Asn 185	Trp	Gly	Tyr	Leu	Asp 190	Gln	Val
Ala	Ala	Leu 195	Arg	Trp	Val	Gln	Gln 200	Asn	Ile	Ala	His	Phe 205	Gly	Gly	Asn
Pro	Asp 210	Arg	Val	Thr	Ile	Phe 215	Gly	Glu	Ser	Ala	Gly 220	Gly	Thr	Ser	Val
Ser 225	Ser	Leu	Val	Val	Ser 230	Pro	Ile	Ser	Gln	Gly 235	Leu	Phe	His	Gly	Ala 240
Ile	Met	Glu	Ser	Gly 245	Val	Ala	Leu	Leu	Pro 250	Gly	Leu	Ile	Ala	Ser 255	Ser

Ala	Asp	Val	260	ser	Thr	Val	Val	265	Asn	Leu	ser	Ala	270	Asp	GIN
Val	Asp	Ser 275	Glu	Ala	Leu	Val	Gly 280	Cys	Leu	Arg	Gly	Lys 285	Ser	Lys	Glu
Glu	Ile 290	Leu	Ala	Ile	Asn	Lys 295	Pro	Phe	Lys	Met	11e 300	Pro	Gly	Val	Val
Asp 305	Gly	Val	Phe	Leu	Pro 310	Arg	His	Pro	Gln	Glu 315	Leu	Leu	Ala	Ser	Ala 320
Asp	Phe	Gln	Pro	Val 325	Pro	Ser	Ile	Val	Gly 330	Val	Asn	Asn	Asn	Glu 335	Phe
Gly	Trp	Leu	Ile 340	Pro	Lys	Val	Met	Arg 345	Ile	Tyr	Asp	Thr	Gln 350	Lys	Glu
Met	Asp	Arg 355	Glu	Ala	Ser	Gln	Ala 360	Ala	Leu	Gln	Lys	Met 365	Leu	Thr	Leu
Leu	Met 370	Leu	Pro	Pro	Thr	Phe 375	Gly	Asp	Leu	Leu	Arg 380	Glu	Glu	Tyr	Ile
Gly 385	Asp	Asn	Gly	Asp	Pro 390	Gln	Thr	Leu	Gln	Ala 395	Gln	Phe	Gln	Glu	Met 400
Met	Ala	Asp	Ser	Met 405	Phe	Val	Ile	Pro	Ala 410	Leu	Gln	Val	Ala	His 415	Phe
Gln	Cys	Ser	Arg 420	Ala	Pro	Val	Tyr	Phe 425	туг	Glu	Phe	Gln	His 430	Gln	Pro
Ser	Trp	Leu 435	Lys	Asn	Ile	Arg	Pro 440	Pro	His	Met	Lys	Ala 445	Asp	His	Gly
-	450		Pro			455	-				460	_		_	
465			Glu		470					475					480
Trp	Ala	Asn	Phe	Ala 485	Arg	Asn	Gly	Asn	Pro 490	Asn	Gly	Glu	Gly	Leu 495	Pro
			Leu 500					505					510		
Gln	Pro	Ala 515	Val	Gly	Arg _.	Ala	Leu 520	Lys	Ala	His	Arg	Leu 525	Gln	Phe	Trp

664

Lys Lys Ala Leu Pro Gln Lys Ile Gln Glu Leu Glu Glu Pro Glu Glu 530 535 540 Arg His Thr Glu Leu 545 <210> 690 <211> 155 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (36) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (46) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (50) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (85) <223> Xaa equals any of the naturally occurring L-amino acids <400> 690 Ser His Arg Val Thr His Cys Pro Tyr Ala Val Ala Leu Pro Glu Val 10 Ala Pro Ala Gln Pro Leu Thr Glu Ala Leu Arg Ala Leu Cys His Val 25 Gly Leu Phe Xaa Phe Ala Phe Cys Ala Leu Phe Asp Cys Xaa Arg Pro 35 40 45 Val Xaa Gln Lys Ser Cys Asp Leu Leu Leu Phe Leu Arg Asp Lys Ile 55 Ala Ser Tyr Ser Ser Leu Arg Glu Ala Arg Gly Ser Pro Asn Thr Ala 65 70 75 Ser Ala Glu Ala Xaa Leu Pro Arg Trp Arg Ala Gly Glu Gln Ala Gln 85 90

Pro Pro Gly Asp Gln Glu Pro Glu Ala Val Leu Ala Met Leu Arg Ser 100 · 105 110

Leu Asp Leu Glu Gly Leu Arg Ser Thr Leu Ala Glu Ser Ser Asp His
115 120 125

Val Glu Lys Ser Pro Gln Ser Leu Leu Gln Asp Met Leu Ala Thr Gly
130 135 140

Gly Phe Leu Gln Gly Asp Glu Ala Asp Cys Tyr 145 150 155

<210> 691

<211> 149

<212> PRT

<213> Homo sapiens

<400> 691

Met Cys Leu Glu Arg Pro Leu Arg Glu Gly Pro Arg Val Met Glu Lys

1 10 15

Glu Ala Trp Pro Gly Ser Leu Glu Gly Arg Gly Gly Gly Trp Arg His 20 25 30

Leu Asp Cys Pro Leu Leu Ser His Thr Trp Gly Val Val Thr Pro Phe

Thr Pro Ala Arg Leu Pro Ser Ala Phe His Glu Leu His Leu Leu Pro 50 60

Thr Ser Leu Trp Arg Gly Trp Gly Pro Leu Ala Ser Thr Arg Gly Pro 65 70 75 80

Ser Ala Ser Pro Lys Pro Glu Pro Ser Ala Pro Gly Glu Asn Lys Trp

Leu Ser Phe Asp Thr Trp Gly Arg Glu Ala Ala Gly Trp Arg Glu 100 105 110

Ser Gln Gly Arg Asp Thr Thr Glu Gly Asp Pro Asp Ile Pro Arg Lys
115 120 125

Phe Pro Ala Glu Gln Thr Ala Phe Gln Pro Glu Ala Cys Leu Asn Cys 130 135 140

Val Met Cys Asn Asn

<21	0> 6	92													
<21	1> 2	18													
<21	2> P	RT									,				
<21	3> н	ото	sapi	ens											
<22	0>														
<22	1> S	ITE													
<22	2> (160)				•									
<22	3> X	aa e	qual	s any	y of	the	nati	ural	ly o	ccur	ring	L-a	mino	acio	ds
<40	0> 6	92													
Pro 1	Gly	Val	Lys	Leu 5	Trp	Asp	Val	Pro	Val 10	Met	Leu	Asp	His	Lys 15	Asp
Leu	Glu	Ala	Glu 20	Ile	His	Pro	Leu	Lys 25	Asn	Glu	Glu	Arg	Lys 30	Ser	Gln
Glu	Asn	Leu 35	Gly	Asn	Pro	Ser	Lys 40	Asn	Glu	Asp	Asn	Val 45	Lys	Ser	Ala
Pro	Pro 50	Gln	Ser	Arg	Leu	Ser 55	Arg	Cys	Arg	Ala	Ala 60	Ala	Phe	Phe	Leu
Ser 65	Leu	Phe	Leu	Cys	Leu 70	Phe	Val	Val	Phe	Val 75	Val	Ser	Phe	Val	Ile 80
Pro	Суз	Pro	Asp	Arg 85	Pro	Ala	Ser	Gln	Arg 90	Met	Trp	Arg	Ile	Asp 95	Tyr
Ser	Ala	Ala	Val 100	Ile	Tyr	Asp	Phe	Leu 105	Ala	Val	Asp	Asp	Ile 110	Asn	Gly
Asp	Arg	Ile 115	Gln	Asp	Val	Leu	Phe 120	Leu	Tyr	Lys	Asn	Thr 125	Asn	Ser	Ser
Asn	Asn 130	Phe	Ser	Arg	Ser	Cys 135	Val	Asp	Glu	Gly	Phe 140	Ser	Ser	Pro	Cys
Thr 145	Phe	Ala	Ala	Ala	Val 150	Ser	Gly	Ala		Ala 155	Ala	Arg	Ser	Gly	Xaa 160
Asp	Leu	Trp	Pro	Lys 165	Thr	Trp	Pro	Ser	Trp 170	Ser	Val	Leu	Cys	Pro 175	Ser
Gln	Glu	Ala	Val 180	Arg	His	Leu	Leu	Pro 185	Ala	Ser	Trp	Trp	Ala 190	Asp	Pro
Val		Ser	Leu	Gln	Ser		Cys	Ser	Gln	Gly	Lys	Pro 205	Trp	Lys	Pro

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Gln Pro Ala Val Gln Gly Glu Trp Ser Ile
    210
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<210> 693
<211> 68
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<213> Homo sapiens
<400> 693
Ser Cys Asn Ser Ser Asn Asn Ile Leu Gln Leu Pro Tyr Arg Asn Arg
Ser Gly Arg Ala Lys Ser Asp Leu Gly Lys Val Ile Arg Tyr Arg Leu
                               25
Ser Ile Pro Phe Pro Lys Met Leu Gly Thr Arg Ser Ile Ser Asp Phe
Ile Ile Phe Phe Lys Val Trp Asn Ile Cys Ile Ile Leu Thr Ser Trp
                         55
Ala Ser Gln Ile
 65
<210> 694
<211> 234
<212> PRT
<213> Homo sapiens
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<223> Xaa equals any of the naturally occurring L-amino acids
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<400> 694
Cys Ala Xaa Xaa Leu Arg Gly Phe Asp Gln Gln Met Ser Ser Met Val
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Ile	Glu	His	Met 20	Ala	Ser	His	Gly	Thr 25	Arg	Phe	Leu	Arg	Gly 30	Суз	Ala
Pro	Ser	Arg 35	Val	Arg	Arg	Leu	Pro 40	Asp	Gly	Gln	Leu	Gln 45	Val	Thr	Trp
Glu	Asp 50	Ser	Thr	Thr	Gly	Lys 55	Glu	Asp	Thr	Gly	Thr 60	Phe	Asp	Thr	Va1
Leu 65	Trp	Ala	Ile	Gly	Arg 70	Val	Pro	Asp	Thr	Arg 75	Ser	Leu	Asn	Leu	Glu 80
Lys	Ala	Gly	Val	Asp 85	Thr	Ser	Pro	Asp	Thr 90	Gln	Lys	Ile	Leu	Val 95	Asp
Ser	Arg	Glu	Ala 100	Thr	Ser	Val	Pro	His 105	Ile	туr	Ala	Ile	Gly 110	Asp	Val
Val	Glu	Gly 115	Arg	Pro	Glu	Leu	Thr 120	Pro	Thr	Ala	Ile	Met 125	Ala	Gly	Arg
Leu	Leu 130	Val	Gln	Arg	Leu	Phe 135	Gly	Gly	Ser	Ser	Asp 140	Leu	Met	Asp	Tyr
Asp 145	Asn	Val	Pro	Thr	Thr 150	Val	Phe	Thr	Pro	Leu 155	Glu	Tyr	Gly	Cys	Val 160
Gly	Leu	Ser	Glu	Glu 165	Glu	Ala	Val	Ala	Arg 170	His	Gly	Gln	Glu	His 175	Val
Glu	Val	Tyr	His 180	Ala	His	Tyr	Lys	Pro 185	Leu	Glu	Phe	Thr	Val 190	Ala	Gly
Arg	Asp	Ala 195	Ser	Gln	Cys	Tyr	Val 200	Lys	Met	Val	Cys	Leu 205	Arg	Glu	Pro
Pro	Gln 210	Leu	Val	Leu	Gly	Leu 215	His	Phe	Leu	Xaa	Pro 220	Thr	Gln	Ala	Asn
Tyr 225	Ser	Arg	Ile	Cys	Ser 230	Gly	Asp	Lys	Cys						

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<211> 460

<212> PRT

<213> Homo sapiens

WO 00/55173

<400	0> 69	95													
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Trp	Ser	Ala	Leu 20	Gly	Trp	Pro	Ala	Ala 25	Leu	Gly	Gly	Gly	Val 30	Val	Ala
Val	Ala	Val 35	Cys	Glu	Pro	Val	Ala 40	Arg	Leu	Leu	Trp	Ala 45	Gly	Thr	Leu
Lys	Ile 50	Ala	Ala	Met	Ala	Glu 55	Asn	Gly	Asp	Asn	Glu 60	Lys	Met	Ala	Ala
Leu 65	Glu	Ala	Lys	Ile	Cys 70	His	Gln	Ile	Glu	Tyr 75	туг	Phe	Gly	Asp	Phe 80
Asn	Leu	Pro	Arg	Asp 85	Lys	Phe	Leu	Lys	Glu 90	Gln	Ile	Lys	Leu	Asp 95	Glu
Gly	Trp	Val	Pro 100	Leu	Glu	Ile	Met	Ile 105	Lys	Phe	Asn	Arg	Leu 110	Asn	Arg
Leu	Thr	Thr 115	Asp	Phe	Asn	Val	Ile 120	Val	Glu	Ala	Leu	Ser 125	Lys	Ser	Lys
Ala	Glu 130	Leu	Met	Glu	Ile	Ser 135	Glu	Asp	Lys	Thr	Lys 140	Ile	Arg	Arg	Ser
Pro 145	Ser	Lys	Pro	Leu	Pro 150	Glu	Val	Thr	Asp	Glu 155	Tyr	Lys	Asn	Asp	Val
Lys	Asn	Arg	Ser	Val 165	Tyr	Ile	Lys	Gly	Phe 170	Pro	Thr	Asp	Ala	Thr 175	Leu
Asp	Asp	Ile	Lys 180	Glu	Trp	Leu	Glu	Asp 185	Lys	Gly	Gln	Val	Leu 190	Asn	Ile
Gln	Met	Arg 195	Arg	Thr	Leu	His	Lys 200	Ala	Phe	Lys	Gly	Ser 205	Ile	Phe	Val
Val	Phe 210	Asp	Ser	Ile	Glu	Ser 215	Ala	Lys	Lys	Phe	Val 220	Glu	Thr	Pro	Gly
G1n 225	Lys	Tyr	Lys	Glu	Thr 230	Asp	Leu	Leu	Ile	Leu 235	Phe	Lys	Asp	Asp	Туг 240
Phe	Ala	Lys	Lys	Asn 245	Glu	Glu	Arg	Lys	Gln 250	Asn	Lys	Val	Glu	Ala 255	Lys
Leu	Arg	Ala	Lys	Gln	Glu	Gln	Glu	Ala 265	Lys	Gln	Lys	Leu	Glu 270	Glu	Asp

Ala	Glu	Met 275	Lys	Ser	Leu	Glu	Glu 280	Lys	Ile	Gly	Cys	Leu 285	Leu	Lys	Phe
Ser	Gly 290	Asp	Leu	Asp	Asp	Gln 295	Thr	Cys	Arg	Glu	Asp 300	Leu	His	Ile	Leu
Phe 305	Ser	Asn	His	Gly	Glu 310	Ile	Lys	Trp	Ile	Asp 315	Phe	Val	Arg	Gly	Ala 320
Lys	Glu	Gly	Ile	11e 325	Leu	Phe	Lys	Glu	Lys 330	Ala	Lys	Glu	Ala	Leu 335	Gly
Lys	Ala	Lys	Asp 340	Ala	Asn	Asn	Gly	Asn 345	Leu	Gln	Leu	Arg	Asn 350	Lys	Glu
Val	Thr	Trp 355	Glu	Val	Leu	Glu	Gly 360	Glu	Val	Glu	Lys	Glu 365	Ala	Leu	Lys
Lys	Ile 370	Ile	Glu	Asp	Gln	Gln 375	Glu	Ser	Leu	Asn	Lys 380	Trp	Lys	Ser	Lys
Gly 385	Arg	Arg	Phe	Lys	Gly 390	Lys	Gly	Lys	Gly	Asn 395	Lys	Ala	Ala	Gln	Pro 400
Gly	Ser	Gly	Lys	Gly 405	Lys	Val	Gln	Phe	Gln 410	Gly	Lys	Lys	Thr	Lys 415	Phe
Ala	Ser	Asp	Asp 420	Glu	His	Asp	Glu	His 425	Asp	Glu	Asn	Gly	Ala 430	Thr	Gly
Pro	Val	Lys 435	Arg	Ala	Arg	Glu	Glu 440	Thr	Asp	Lys	Glu	Glu 445	Pro	Ala	Ser
Lys	Gln 450	Gln	Lys	Thr	Glu	Asn 455	Gly	Ala	Gly	Asp	Gln 460				

<210> 696

<211> 80

<212> PRT

<213> Homo sapiens

Gly Glu Glu Gly Val Gly Ser Pro Ser Gly Ile Leu Ala Thr Pro Leu 10

Arg Ser Ala Arg Gly Thr Thr His Thr His Thr His Thr His Thr His 20 25

Thr His Ser His Thr His Ala His Phe Pro Ser Phe Pro Asp Pro Leu 45 35 40

Phe Gln Ser Ser Pro Phe Ser Ser Gly Phe Ile Asp Glu Tyr Lys Tyr

Pro His Leu Trp Pro Val Met Ser Val Thr Cys Cys Arg Phe Cys Val 70 75

<210> 697

<211> 257

<212> PRT

<213> Homo sapiens

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Trp Pro Arg Arg Pro Gly Pro His Leu Gly Val Leu Glu Phe Pro Gly

Ala Gly Cys Gly Ala Ser Ala Ala Gly Trp Pro Ser Ala Xaa Met Leu 25

Pro Gly Arg Gly Pro Arg Pro Phe Arg Ala Arg Leu Val Gly Arg Glu 35

Leu Val Ser Met Leu Ala Arg Glu Leu Pro Ala Ala Val Ala Pro Ala 55

Gly Pro Ala Ser Leu Ala Arg Trp Thr Leu Gly Phe Cys Asp Glu Arg 75

Leu Val Pro Phe Asp His Ala Glu Ser Thr Tyr Gly Leu Tyr Arg Thr 85

His Leu Leu Ser Arg Leu Pro Ile Pro Glu Ser Gln Val Ile Thr Ile 105

Asn Pro Glu Leu Pro Val Glu Glu Ala Ala Glu Asp Tyr Ala Lys Lys 115 120

Leu Arg Gln Ala Phe Gln Gly Asp Ser Ile Pro Val Phe Asp Leu Leu 135 130

672

Ile Leu Gly Val Gly Pro Asp Gly His Thr Cys Ser Leu Phe Pro Asp
145 150 155 160

His Pro Leu Leu Gln Glu Arg Glu Lys Ile Val Ala Pro Ile Ser Asp 165 170 175

Ser Pro Lys Pro Pro Pro Gln Arg Val Thr Leu Thr Leu Pro Val Leu 180 185 190

Asn Ala Ala Arg Thr Val Ile Phe Val Ala Thr Gly Glu Gly Lys Ala 195 200 205

Ala Val Leu Lys Arg Ile Leu Glu Asp Gln Glu Glu Asn Pro Leu Pro 210 215 220

Ala Ala Leu Val Gln Pro His Thr Gly Lys Leu Cys Trp Phe Leu Asp 225 230 235 240

Glu Ala Ala Arg Leu Leu Thr Val Pro Phe Glu Lys His Ser Thr 245 250 255

Leu

<210> 698

<211> 68

<212> PRT

<213> Homo sapiens

<400> 698

Gln Tyr Lys Thr Pro Ala Val Asp Thr Thr Met Met Thr Phe His Glu

1 5 10 15

Leu Val Phe Leu Val Leu Thr Ala Lys Phe Val Leu Phe Thr Gly Gln 20 25 30

Ile Ser Asn Lys Val Leu Gly Leu Lys Ile His Gly Trp Thr Glu Val 35 40 45

Pro Tyr Pro Leu Thr Met Glu Ala Gly Ala Thr Phe Trp Gly Tyr Leu 50 55 60

Phe Leu Asn Phe

<21	1- 3 2> Р 3> н	RT	sapi	ens											
			Jupi	00											
	_		Ala	Thr 5	Thr	Ala	Trp	Val	Lys 10	Ser	Ser	Ile	Lys	Thr 15	His
Leu	Cys	Ala	Ser 20	Leu	Arg	His	Ile	Arg 25	Phe	Leu	Leu	Ser	Val 30	Cys	Leu
Leu	Cys	Leu 35	Val	Ala	Gly	Thr	Ala 40	Val	Ala	Val	Lys	Met 45	Ala	Ser	Thr
Ser	Arg 50	Leu	Asp	Ala	Leu	Pro 55	Arg	Val	Thr	Cys	Pro 60	Asn	His	Pro	Asp
Ala 65	Ile	Leu	Val	Glu	Asp 70	Tyr	Arg	Ala	Gly	Asp 75	Met	Ile	Cys	Pro	Glu 80
Суѕ	Gly	Leu	Val	Val 85	Gly	Asp	Arg	Val	Ile 90	Asp	Val	Gly	Ser	Glu 95	Trp
Arg	Thr	Phe	Ser 100	Asn	Asp	Lys	Ala	Thr 105	Lys	Asp	Pro	Ser	Arg 110	Val	Gly
Asp	Ser	Gln 115	Asn	Pro	Leu	Leu	Ser 120	Asp	Gly	Asp	Leu	Ser 125	Thr	Met	Ile
Gly	Lys 130	Gly	Thr	Gly	Ala	Ala 135	Ser	Phe	Asp	Glu	Phe 140	Gly	Asn	Ser	Lys
Tyr 145	Gln	Asn	Arg	Arg	Thr 150	Met	Ser	Ser	Ser	Asp 155	Arg	Ala	Met	Met	Asn 160
Ala	Phe	Lys	Glu	Ile 165	Thr	Thr	Met	Ala	Asp 170	Arg	Ile	Asn	Leu	Pro 175	Arg
Asn	Ile	Val	Asp 180	Arg	Thr	Asn	Asn	Leu 185	Phe	Lys	Gln	Val	Tyr 190	Glu	Gln
Lys	Ser	Leu 195	Lys	Gly	Arg	Ala	Asn 200	Asp	Ala	Ile	Ala	Ser 205	Ala	Cys	Leu
Tyr	Ile 210	Ala	Суз	Arg	Gln	Glu 215	Gly	Val	Pro	Arg	Thr 220	Phe	Lys	Glu	Ile
Cys 225	Ala	Val	Ser	Arg	11e 230	Ser	Lys	Lys	Glu	Ile 235	Gly	Arg	Суз	Phe	Lys 240
Leu	Ile	Leu	Lys	Ala	Leu	Glu	Thr	Ser	Val	Asp	Leu	Ile	Thr	Thr	Gly

245 250 255 Asp Phe Met Ser Arg Phe Cys Ser Asn Leu Cys Leu Pro Lys Gln Val 265 Gln Met Ala Ala Thr His Ile Ala Arg Lys Ala Val Glu Leu Asp Leu 275 280 Val Pro Gly Arg Ser Pro Ile Ser Val Ala Ala Ala Ala Ile Tyr Met 295 Ala Ser Gln Ala Ser Ala Glu Lys Arg Thr Gln Lys Glu Ile Gly Asp 310 315 Ile Ala Gly Val Ala Asp Val Thr Ile Arg Gln Ser Tyr Arg Leu Ile 325 330 Tyr Pro Arq Ala Pro Asp Leu Phe Pro Thr Asp Phe Lys Phe Asp Thr 345 Pro Val Asp Lys Leu Pro Gln Leu 355 360 <210> 700 <211> 364 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (13) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (30) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (353) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (360) <223> Xaa equals any of the naturally occurring L-amino acids

<400> 700

PCT/US00/05881 WO 00/55173

675

Pro Ser Trp Leu Arg Ala Arg Ser Ser Arg Ser Trp Xaa Ala Ser Pro 5 10

- Arg Gly Pro Gln Pro Pro Arg Ile Arg Ala Arg Ser Ala Xaa Pro Met
- Glu Gly Ala Arg Val Phe Gly Ala Leu Gly Pro Ile Gly Pro Ser Ser
- Pro Gly Leu Thr Leu Gly Gly Leu Ala Val Ser Glu His Arg Leu Ser
- Asn Lys Leu Leu Ala Trp Ser Gly Val Leu Glu Trp Gln Glu Lys Arg
- Arg Pro Tyr Ser Asp Ser Thr Ala Lys Leu Lys Arg Thr Leu Pro Cys
- Gln Ala Tyr Val Asn Gln Gly Glu Asn Leu Glu Thr Asp Gln Trp Pro 100 105
- Gln Lys Leu Ile Met Gln Leu Ile Pro Gln Gln Leu Leu Thr Thr Leu 120
- Gly Pro Leu Phe Arg Asn Ser Gln Leu Ala Gln Phe His Phe Thr Asn 135
- Arg Asp Cys Asp Ser Leu Lys Gly Leu Cys Arg Ile Met Gly Asn Gly 145
- Phe Ala Gly Cys Met Leu Phe Pro His Ile Ser Pro Cys Glu Val Arg 170
- Val Leu Met Leu Leu Tyr Ser Ser Lys Lys Ile Phe Met Gly Leu
- Ile Pro Tyr Asp Gln Ser Gly Phe Val Ser Ala Ile Arg Gln Val Ile
- Thr Thr Arg Lys Gln Ala Val Gly Pro Gly Gly Val Asn Ser Gly Pro
- Val Gln Ile Val Asn Asn Lys Phe Leu Ala Trp Ser Gly Val Met Glu 225
- Trp Gln Glu Pro Arg Pro Glu Pro Asn Ser Arg Ser Lys Arg Trp Leu
- Pro Ser His Val Tyr Val Asn Gln Gly Glu Ile Leu Arg Thr Glu Gln

Trp Pro Arg Lys Leu Tyr Met Gln Leu Ile Pro Gln Gln Leu Leu Thr 275 280 Thr Leu Val Pro Leu Phe Arg Asn Ser Arg Leu Val Gln Phe His Phe 295 Thr Lys Asp Leu Glu Thr Leu Lys Ser Leu Cys Arg Ile Met Asp Asn Gly Phe Ala Gly Cys Val His Phe Ser Tyr Lys Ala Ser Cys Glu Ile 325 Arg Val Leu Met Leu Leu Tyr Ser Ser Glu Lys Lys Ile Phe Ile Gly Xaa Ile Pro His Asp Gln Gly Xaa Phe Val Gln Arg <210> 701 <211> 156 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (33) <223> Xaa equals any of the naturally occurring L-amino acids Gly Thr Arg Gly Ile Leu His Val Ala Val Pro Ala Arg Gly Thr His 10 Ala Gln Cys Cys Arg Asn Trp Thr Val Pro Asp Ser Gly Gln Gly Lys 25 Xaa Val Met Leu Glu Gly Gln Gly Arg Leu Glu Arg Val His Ile Pro 40 Leu Ser Ala Pro Ala Ser Ala Thr Val Gln Arg Pro Thr Gly Pro Gln 50 Pro Val Ala Cys Pro His Cys Pro Val Pro Thr Ser Asn Ser Pro Gln 70 75 Pro Leu Val Ala Ser Val Pro Cys Pro Leu Gly Phe Ser Ser Gln Pro 90 85

Ser Gly Leu Gly Leu Cys Arg Lys Val Met Pro Thr Gly Thr Leu Leu 105

Thr Pro Gly Ser Phe Met Asp Val Val Ser Glu Leu Arg Thr Arg Gly
115 120 125

Cys Gln Met Phe Leu Ala Pro His Val Ser Phe Arg Thr Glu Gln Lys 130 135 140

His Lys Asp Ser Ala Lys Ser Ser Leu Tyr Ser Leu 145 150 155

<210> 702

<211> 150

<212> PRT

<213> Homo sapiens

<400> 702

Ala Gly His Gly Leu Gly Val Arg Ala Gly Leu Lys Glu Phe Ala Thr
1 5 10 15

Asn Leu Thr Glu Ser Gly Val His Gly Ala Leu Leu Ala Leu Asp Glu 20 25 30

Thr Phe Asp Tyr Ser Asp Leu Ala Leu Leu Gln Ile Pro Thr Gln
35 40 45

Asn Ala Gln Ala Arg Gln Leu Leu Glu Lys Glu Phe Ser Asn Leu Ile $50 \hspace{1cm} 55 \hspace{1cm} 60$

Ser Leu Gly Thr Asp Arg Arg Leu Asp Glu Asp Ser Ala Lys Ser Phe
65 70 75 80

Ser Arg Ser Pro Ser Trp Arg Lys Met Phe Arg Glu Lys Asp Leu Arg 85 90 95

Gly Val Thr Pro Asp Ser Ala Glu Met Leu Pro Pro Asn Phe Arg Ser 100 105 110

Ala Ala Ala Gly Ala Leu Gly Ser Pro Gly Leu Pro Leu Arg Lys Leu 115 120 125

Gln Pro Glu Gly Gln Thr Ser Gly Ser Ser Arg Ala Asp Gly Val Ser 130 135 140

Val Arg Thr Tyr Ser Cys 145 150

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<211> 527
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<400> 703
Cys Val Cys Val Glu Gly Val Glu Gly Pro Arg Cys Asp Lys Cys Thr
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Arg	Gly	Tyr	Ser 20	Gly	Val	Phe	Pro	Asp 25	CÀa	Thr	Pro	Cys	His 30	Gln	Cys
Phe	Ala	Leu 35	Trp	Asp	Val	Ile	Ile 40	Ala	Glu	Leu	Thr	Asn 45	Arg	Thr	His
Arg	Phe 50	Leu	Glu	Lys	Ala	Lys 55	Ala	Leu	Lys	Ile	Ser 60	Gly	Val	Ile	Gly
Pro 65	Tyr	Arg	Glu	Thr	Val 70	Asp	Ser	Val	Glu	Arg 75	Lys	Val	Ser	Glu	Ile 80
Lys	Asp	Ile	Leu	Ala 85	Gln	Ser	Pro	Ala	Ala 90	Glu	Pro	Leu	Lys	Asn 95	Ile
Gly	Asn	Leu	Phe 100	Glu	Glu	Ala	Glu	Lys 105	Leu	Ile	Lys	Asp	Val 110	Thr	Glu
Met	Met	Ala 115	Gln	Val	Glu	Val	Lys 120	Leu	Ser	Asp	Thr	Thr 125	Ser	Gln	Ser
Asn	Ser 130	Thr	Ala	Lys	Glu	Leu 135	Asp	Ser	Leu	Gln	Thr 140	Glu	Ala	Glu	Ser
Leu 145	Asp	Asn	Thr	Val	Lys 150	Glu	Leu	Ala	Glu	Gln 155	Leu	Glu	Phe	Ile	Lys 160
Asn	Ser	Asp	Ile	Arg 165	Gly	Ala	Leu	Asp	Ser 170	Ile	Thr	Lys	Tyr	Phe 175	Gln
Met	Ser	Leu	Glu 180	Ala _.	Glu	Glu	Arg	Val 185	Asn	Ala	Ser	Thr	Thr 190	Glu	Pro
Asn	Ser	Thr 195	Val	Glu	Gln	Ser	Ala 200	Leu	Met	Arg	Asp	Arg 205	Val	Glu	Asp
Val	Met 210	Met	Glu	Arg	Glu	Ser 215	Gln	Phe	Lys	Glu	Lys 220	Gln	Glu	Glu	Gln
Ala 225	Arg	Leu	Leu	Asp	Glu 230	Leu	Ala	Gly	Lys	Leu 235	Gln	Ser	Leu	Asp	Leu 240
Ser	Ala	Xaa	Ala	Glu 245	Met	Thr	Cys	Gly	Thr 250	Pro	Pro	Gly	Ala	Ser 255	Cys
Xaa	Glu	Xaa	Glu 260	Cys	Gly	Gly	Pro	Asn 265	Cys	Arg	Thr	Asp	Glu 270	Gly	Glu
Arg	Lys	Cys	Gly	Gly	Pro	Gly	Cys	Gly	Gly	Leu	Val	Thr	Val	Ala	His

		275					280					285			
Asn	Ala 290	Trp	Gln	Lys	Ala	Met 295	Asp	Leu	Asp	Gln	Asp 300	Val	Leu	Ser	Ala
Leu 305	Ala	Glu	Val	Glu	Gln 310	Leu	Ser	Lys	Met	Val 315	Ser	Glu	Ala	Lys	Leu 320
Arg	Ala	Asp	Glu	Ala 325	Lys	Gln	Ser	Ala	Glu 330	Asp	Ile	Leu	Leu	Lys 335	Thr
Asn	Ala	Thr	Lys 340	Glu	Lys	Met	Asp	Lys 345	Ser	Asn	Glu	Glu	Leu 350	Arg	Asn
Leu	Ile	Lys 355	Gln	Ile	Arg	Asn	Phe 360	Leu	Thr	Gln	Asp	Ser 365	Ala	Asp	Leu
Asp	Ser 370	Ile	Glu	Ala	Val	Ala 375	Asn	Glu	Val	Leu	Lys 380	Met	Glu	Met	Pro
Ser 385	Thr	Pro	Gln	Gln	Leu 390	Gln	Asn	Leu	Thr	Glu 395	Asp	Ile	Arg	Glu	Arg 400
Val	Glu	Ser	Leu	Ser 405	Gln	Val	Glu		Ile 410	Leu	Gln	His	Ser	Ala 415	Ala
Asp	Ile	Ala	Arg 420	Ala	Glu	Met	Leu	Leu 425	Glu	Glu	Ala	Lys	Arg 430	Ala	Ser
Lys	Ser	Ala 435	Thr	Asp	Val	Lys	Val 440	Thr	Ala	Asp	Met	Val 445	Lys	Glu	Ala
Leu	Glu 450	Glu	Ala	Glu	Lys	Ala 455	Gln	Val	Ala	Ala	Glu 460	Lys	Ala	Ile	Lys
Gln 465	Ala	Asp	Glu	Asp	Ile 470	Xaa	Arg	Asn	Pro	Glu 475	Pro	Xaa	Asn	Phe	Xaa 480
Leu	Glu	Phe	Xaa	Lys 485	Gln	Gln	Leu	Ser	Gly 490	Gly	Asn	Leu	Val	Gln 495	Arg
Val	Pro	Arg	Ala 500	Ser	Ser	Glu	Phe	Arg 505	Glu	Asp	Val	Gly	Arg 510	Xaa	Leu
Ser	Gly	Lys 515	Leu	Ala	Gln	Xaa	Pro 520	Gly	Gly	Gly	Arg	Ile 525	Phe	Trp	

PCT/US00/05881 WO 00/55173

681

<212> PRT

<213> Homo sapiens

<400> 704

Val Tyr Gln Arg Lys Ser Thr Val Val Leu Gly Gly Phe Leu Leu Trp 1 5

Asp Ile Asp Phe Leu Phe Phe Phe Arg Asn Ile Val Cys Cys Asn Leu 25

Asn Lys Asn Tyr Asp Ile Leu Arg Tyr Phe Ile Asp Lys Pro Asn Lys 40

Asn Ile Cys Phe Tyr Phe Lys Val Asn Val Phe Leu Phe Ser 55

<210> 705

<211> 44

<212> PRT

<213> Homo sapiens

<400> 705

Thr Glu Asp Leu Phe Gly Phe Lys His Leu Leu Arg Gln Tyr Leu Leu

Gly Lys Pro Asn Ile Ala Asn Gly Gln Phe Asp Phe Asn Phe Ser Lys

Asp Thr Leu Leu Ser Arg Arg Leu Lys Cys Leu His

<210> 706

<211> 193

<212> PRT

<213> Homo sapiens

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<400> 706

Xaa Gly Arg Ala Trp Val Met Ala Ala Pro Gly Ala Leu Leu Val Met 5 10

Gly Val Ser Gly Ser Gly Lys Ser Thr Val Gly Ala Leu Leu Ala Ser 20 25

682

Glu Leu Gly Trp Lys Phe Tyr Asp Ala Asp Asp Tyr His Pro Glu Glu
35 40 45

Asn Arg Arg Lys Met Gly Lys Gly Ile Pro Leu Asn Asp Gln Asp Arg 50 55 60

Ile Pro Trp Leu Cys Asn Leu His Asp Ile Leu Leu Arg Asp Val Ala 65 70 75 80

Ser Gly Gln Arg Val Val Leu Ala Cys Ser Ala Leu Lys Lys Thr Tyr
85 90 95

Arg Asp Ile Leu Thr Gln Gly Lys Asp Gly Val Ala Leu Lys Cys Glu 100 105 110

Glu Ser Gly Lys Glu Ala Lys Gln Ala Glu Met Gln Leu Leu Val Val
115 120 125

His Leu Ser Gly Ser Phe Glu Val Ile Ser Gly Arg Leu Leu Lys Arg 130 135 140

Glu Gly His Phe Met Pro Pro Glu Leu Leu Gln Ser Gln Phe Glu Thr 145 150 155 160

Leu Glu Pro Pro Ala Ala Pro Glu Asn Phe Ile Gln Ile Ser Val Asp 165 170 175

Lys Asn Val Ser Glu Ile Ile Ala Thr Ile Met Glu Thr Leu Lys Met 180 185 190

Lys

<210> 707

<211> 121

<212> PRT

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<223> Xaa equals any of the naturally occurring L-amino acids

<220> '

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683

<40	0> 70	07													
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Trp	Pro	Leu	Gly 20	Ala	Leu	Glu	Thr	Ser 25	His	Val	Leu	Trp	Ala 30	Leu	Tr
Arg	Ala	Leu 35	Ala	Leu	His	Gly	Gly 40	Ala	Gly	Arg	His	Cys 45	Leu	Pro	Cy
Pro	Leu 50	Pro	Ala	Ala	Pro	Ala 55	Leu	Val	Cys	Arg	Leu 60	Gly	Pro	Gly	СУ
Leu 65	Leu	Leu	Gly	Val	Trp 70	Pro	Arg	Ala	Pro	Val 75	Lys	Pro	Trp	Arg	Hi:
Cys	Val	Суѕ	Val	Met 85	Gly	Ser	Glu	Gly	Leu 90	Val	Gly	Ala	Val	His 95	Tr
Ser	Ser	Ser	Leu 100	Pro	Xaa	Xaa	Ala	Ile 105	Ser	Met	Ala	Pro	Phe 110	Ala	Ala
Glu	Asp	Thr 115	His	Cys	Gly	Ser	Val 120	Gly	V						
<210)> 70	18													
	l> 11														
<212	2> PF	₹T													
<213	3> Hc	omo s	sapie	ens											
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			Суз	Tyr 5	Phe	His	Ile	Arg	Val 10	Gln	Thr	Tyr	Lys	Gly 15	Ala
Cys	Ser	Leu	Lys 20	Val			Tyr			Ser	Val	Суз	Leu 30	Tyr	Сy
Tyr	Arg	Met 35	Leu	Cys	Phe	Gly	Ala 40	Leu	Ser	Ser	Ala	Asp 45	Pro	Arg	Se
Ser	Val 50	Glu	Ile	His	Cys	Leu 55	Gly	His	Ser	Leu	Ile 60	Arg	Met	Leu	Ala

Gly Asp Phe Val Ser Asp Val Ala Ser Leu Phe Ser Val His Arg Leu

Arg Val Thr Thr Val Ala Cys Arg Val His Pro Val Gly Ala Ala Gln

684

Leu Ser Glu Ser Lys Asn Leu Pro Thr Tyr Ser Asn Val Phe Ala Leu 100 105 110

<210> 709

<211> 72

<212> PRT

<213> Homo sapiens

<400> 709

Arg Arg Val Trp Val Leu Phe Pro Pro Gln Arg Pro Glu Ser Gly Trp 1 5 10 15

Gly Val Ser Pro Val Glu Gly Glu Thr Val Pro Ala Leu Arg Gly Met 20 25 30

Lys Lys Ser Val Gly Leu Pro Val Ala Val Gln Cys Val Ala Leu Pro 35 40 45

Trp Gln Glu Glu Leu Cys Leu Arg Phe Met Arg Glu Val Glu Arg Leu 50 55 60

Met Thr Pro Glu Lys Gln Ser Ser 65 70

<210> 710

<211> 84

<212> PRT

<213> Homo sapiens

<400> 710

Arg Leu His Arg Tyr Pro Glu Ala Met Ala Ser Lys Gly Leu Gln Asp

Leu Lys Gln Gln Val Glu Gly Thr Ala Gln Glu Ala Val Ser Ala Ala 20 25 30

Gly Ala Ala Gln Gln Val Val Asp Gln Ala Thr Glu Ala Gly Gln
35 40 45

Lys Ala Met Asp Gln Leu Ala Lys Thr Thr Gln Glu Thr Ile Asp Lys 50 55 60

Thr Ala Asn Gln Ala Ser Asp Thr Phe Ser Gly Ile Gly Lys Lys Phe
65 70 75 80

685

Gly Leu Leu Lys

<210> 711

<211> 63

<212> PRT

<213> Homo sapiens

<400> 711

Arg Leu His Arg Tyr Pro Glu Ala Met Ala Ser Lys Gly Leu Gln Asp 1 5 10 15

Leu Lys Gln Gln Val Glu Gly Thr Ala Gln Glu Ala Ala Met Asp Gln 20 25 30

Leu Ala Lys Thr Thr Gln Glu Thr Ile Asp Lys Thr Ala Asn Gln Ala $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$

Ser Asp Thr Phe Ser Gly Ile Gly Lys Lys Phe Gly Leu Leu Lys 50 60

<210> 712

<211> 86

<212> PRT

<213> Homo sapiens

<400> 712

Arg Leu Ala Asn Arg Ala Ile Met Ser His Lys Gln Ile Tyr Tyr Ser $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$

Asp Lys Tyr Asp Asp Glu Glu Phe Glu Tyr Arg His Val Met Leu Pro 20 25 30

Lys Asp Ile Ala Lys Leu Val Pro Lys Thr His Leu Met Ser Glu Ser 35 40 45

Glu Trp Arg Asn Leu Gly Val Gln Gln Ser Gln Gly Trp Val His Tyr 50 60

Met Ile His Glu Pro Glu Pro His Ile Leu Leu Phe Arg Arg Pro Leu 65 70 75 80

Pro Lys Lys Pro Lys Lys

686

<210> 713 <211> 193 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (129) <223> Xaa equals any of the naturally occurring L-amino acids Val Gln Lys Ala Gly Ala Arg Ala Leu Ala Val Ala Gly Ala Ala Arg Thr Pro Arg Ser Leu Pro Gly Arg Pro Ala Val Cys Asn Met Thr Leu 25 Glu Glu Phe Ser Ala Gly Glu Gln Lys Thr Glu Arg Met Asp Lys Val Gly Asp Ala Leu Glu Glu Val Leu Ser Lys Ala Leu Ser Gln Arg Thr Ile Thr Val Gly Val Tyr Glu Ala Ala Lys Leu Leu Asn Val Asp Pro 70 75 Asp Asn Val Val Leu Cys Leu Leu Ala Ala Asp Glu Asp Asp Asp Arg 85 90 Asp Val Ala Leu Gln Ile His Phe Thr Leu Ile Gln Ala Phe Cys Cys 105 Glu Asn Asp Ile Asn Ile Leu Arg Val Thr Thr Arg Ala Gly Trp Arg 115 120 Maa Pro Ala Leu Gly Asp Arg Arg Trp Pro Arg Gly Glu Arg Gly Arg 135 Arg Ala Ala Pro Gly Pro Ala Leu Arg Val Val Thr Asn Pro His Ser 150 155 Ser Gln Trp Lys Asp Pro Ala Leu Ser Gln Leu Ile Cys Phe Cys Arg 165 Glu Ser Arg Tyr Met Asp Gln Trp Val Pro Val Ile Asn Leu Pro Glu

185

190

Arg

PCT/US00/05881 WO 00/55173

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<210> 714
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 Ser Val Lys Cys Glu Pro Arg Arg Gly Arg Ile Trp Pro Gly Ala
 Gly Gly Val Gly Ala Ala Arg His Val His His Gln Gly Ala
 Gln Gln Ala Gly Arg Ala Ala Pro His Arg Ser His Ala Ala Ala Gly
 Gly Gly Pro Ala Arg Arg Ala Pro Glu Met Pro Ala Ala Arg Ala Ala
                      70
                                         75
 Asp Leu Ala Ala Pro Ala Gly Ala Ala Xaa Cys Ala Xaa Pro Gly Pro
 Trp Pro Leu Ser Ser Pro Gly Pro Arg Leu Val Phe Asn Arg Val Asn
 Gly Arg Arg Ala Pro Ser Thr Ser Pro Ser Phe Glu Gly Thr Gln Glu
 Thr Tyr Thr Val Ala His Glu Glu Asn Val Arg Phe Val Ser Glu Ala
     130
                         135
                                            140
 Trp Gln Gln Val Gln Gln Leu Asp Gly Gly Pro Ala Gly Glu Gly
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155 160 145 150 Gly Pro Arg Pro Val Gln Tyr Val Glu Arg Thr Pro Asn Pro Arg Leu 165 170 Gln Asn Phe Val Pro Ile Asp Leu Asp Glu Trp Trp Ala Xaa Gln Phe 185 180 Leu Ala Arg Ile Thr Ser Cys Ser 195 <210> 715 <211> 106 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (15) <223> Xaa equals any of the naturally occurring L-amino acids <400> 715 Trp Ile Pro Arg Ala Ala Gly Ile Arg His Glu Leu Val Pro Xaa Leu Trp Ser Arg Glu Glu Ala Met Ala Thr Met Glu Asn Lys Val Ile Cys Ala Leu Val Leu Val Ser Met Leu Ala Leu Gly Thr Leu Ala Glu Ala Gln Thr Glu Thr Cys Thr Val Ala Pro Arg Glu Arg Gln Asn Cys Gly 55 60 Phe Pro Gly Val Thr Pro Ser Gln Cys Ala Asn Lys Gly Cys Cys Phe Asp Asp Thr Val Arg Gly Val Pro Trp Cys Phe Tyr Pro Asn Thr Ile

<210> 716 <211> 105 <212> PRT <213> Homo sapiens

Asp Val Pro Pro Glu Glu Glu Cys Glu Phe

<400> 716 Glu Gly Arg Glu Ala Gly Ser Gly Leu Ser Val Asp Ser Arg Asp Lys 10 Gly His Glu Gly Arg Gly Leu Gly Pro Phe Arg Ile Pro Gln Asp Ser 25 Gln Val Gln Leu Cys Gln Lys Gly Thr Phe His Val Met Gln Leu Arg Gly Leu Ser Leu Asn Pro Arg Leu Leu Thr Leu Gly Ser Phe Asn 55 Gln Val Gly Gln Pro Leu Leu Gln Arg Gly Val Gly Trp Leu Ser Ser Leu Ser His Ala Ala Cys Glu Asp Arg Gly Gly Gly Val Gly Ser Gly Lys Ser Pro Glu Asn Arg Arg Gly Ile <210> 717 <211> 431 <212> PRT <213> Homo sapiens Arg Ala Ala Gly Ile Arg His Glu Arg Gly Gly Pro Thr Gly Ser Cys Pro Gly Leu Pro Ser Pro Pro Met Val Leu Tyr Ile Lys Tyr Pro Gly Trp Arg Ser His Met Leu Leu Thr Glu Gly Gly Asn Tyr His Ser Ser 40 Leu Gly Thr Arg Cys Glu Leu Ser Cys Asp Arg Gly Phe Arg Leu Ile Gly Arg Arg Ser Val Gln Cys Leu Pro Ser Arg Arg Trp Ser Gly Thr Ala Tyr Cys Arg Gln Met Arg Cys His Ala Leu Pro Phe Ile Thr Ser Gly Thr Tyr Thr Cys Thr Asn Gly Val Leu Leu Asp Ser Arg Cys Asp

105

110

Tyr	Ser	Cys 115	Ser	Ser	Gly	Tyr	His 120	Leu	Glu	Gly	Asp	Arg 125	Ser	Arg	Ile
Cys	Met 130	Glu	Asp	Gly	Arg	Trp 135	Ser	Gly	Gly	Glu	Pro 140	Val	Cys	Val	Asp
Ile 145	Asp	Pro	Pro	Lys	11e 150	Arg	Cys	Pro	His	Ser 155	Arg	Glu	Lys	Met	Ala 160
Glu	Pro	Glu	Lys	Leu 165	Thr	Ala	Arg	Val	Tyr 170	Trp	Asp	Pro	Pro	Leu 175	Val
Lys	Asp	Ser	Ala 180	Asp	Gly	Thr	Ile	Thr 185	Arg	Val	Thr	Leu	Arg 190	Gly	Pro
Glu	Pro	Gly 195	Ser	His	Phe	Pro	Glu 200	Gly	Glu	His	Val	Ile 205	Arg	Tyr	Thr
Ala	Tyr 210	Asp	Arg	Ala	Tyr	Asn 215	Arg	Ala	Ser	Cys	Lys 220	Phe	Ile	Val	Lys
Val 225	Gln	Val	Arg	Arg	Cys 230	Pro	Thr	Leu	Lys	Pro 235	Pro	Gln	His	Gly	Tyr 240
Leu	Thr	Суз	Thr	Ser 245	Ala	Gly	Asp	Asn	Tyr 250	Gly	Ala	Thr	Cys	Glu 255	Туг
His	Cys	Asp	Gly 260	Gly	Tyr	Asp	Arg	Gln 265	Gly	Thr	Pro	Ser	Arg 270	Val	Cys
Gln	Ser	Ser 275	Arg	Gln	Trp	Ser	Gly 280	Ser	Pro	Pro	Ile	Cys 285	Ala	Pro	Met
Lys	Ile 290	Asn	Val	Asn	Val	Asn 295	Ser	Ala	Ala	Gly	Leu 300	Leu	Asp	Gln	Phe
Tyr 305	Glu	Lys	Gln	Arg	Leu 310	Leu	Ile	Ile	Ser	Ala 315	Pro	Asp	Pro	Ser	Asn 320
Arg	Tyr	Tyr	Lys	Met 325	Gln	Ile	Ser	Met	Leu 330	Gln	Gln	Ser	Thr	Cys 335	Gly
Leu	Asp	Leu	Arg 340	His	Val	Thr	Ile	11e 345	Glu	Leu	Val	Gly	Gln 350	Pro	Pro
Gln	Glu	Val 355	Gly	Arg	Ile	Arg	Glu 360	Gln	Gln	Leu	Ser	Ala 365	Asn	Ile	Ile
Glu	Glu 370	Leu	Arg	Gln	Phe	Gln 375	Arg	Leu	Thr	Arg	Ser 380	Tyr	Phe	Asn	Met

Val Leu Ile Asp Lys Gln Gly Ile Asp Arg Asp Arg Tyr Met Glu Pro Val Thr Pro Glu Glu Ile Phe Thr Phe Ile Asp Asp Tyr Leu Leu Ser Asn Gln Glu Leu Thr Gln Arg Arg Glu Gln Arg Asp Ile Cys Glu 425 <210> 718 <211> 417 <212> PRT <213> Homo sapiens <400> 718 Gln Gly Leu Pro Asp Gly Val Trp Ala His Gly Thr Cys Pro Gly His Arg Leu Val Ser Ser Gln Arg Arg Ile Ile Ala Ser Gly Ser Glu Asp 25 Cys Thr Val Met Val Trp Gln Ile Pro Glu Asn Gly Leu Thr Ser Pro Leu Thr Glu Pro Val Val Leu Glu Gly His Thr Lys Arg Val Gly Ile Ile Ala Trp His Pro Thr Ala Arg Asn Val Leu Leu Ser Ala Gly 70 Cys Asp Asn Val Val Leu Ile Trp Asn Val Gly Thr Ala Glu Glu Leu Tyr Arg Leu Asp Ser Leu His Pro Asp Leu Ile Tyr Asn Val Ser Trp 105 Asn His Asn Gly Ser Leu Phe Cys Ser Ala Cys Lys Asp Lys Ser Val 115 120 Arg Ile Ile Asp Pro Arg Arg Gly Thr Leu Val Ala Glu Arg Glu Lys 130 135 Ala His Glu Gly Ala Arg Pro Met Arg Ala Ile Phe Leu Ala Asp Gly Lys Val Phe Thr Thr Gly Phe Ser Arg Met Ser Glu Arg Gln Leu Ala

170

Leu	Trp	Asp	Pro 180	Glu	Asn	Leu	Glu	Glu 185	Pro	Met	Ala	Leu	Gln 190	Glu	Leu
Asp	Ser	Ser 195	Asn	Gly	Ala	Leu	Leu 200	Pro	Phe	Tyr	Asp	Pro 205	Asp	Thr	Ser
Val	Val 210	Tyr	Val	Суѕ	Gly	Lys 215	Gly	Asp	Ser	Ser	Ile 220	Arg	Tyr	Phe	Glu
Ile 225	Thr	Glu	Glu	Pro	Pro 230	Tyr	Ile	His	Phe	Leu 235	Asn	Thr	Phe	Thr	Ser 240
Lys	Glu	Pro	Gln	Arg 245	Gly	Met	Gly	Ser	Met 250	Pro	Lys	Arg	Gly	Leu 255	Glu
Val	Ser	Lys	Cys 260	Glu	Ile	Ala	Arg	Phe 265	Tyr	Lys	Leu	His	Glu 270	Arg	Lys
_		275					Val 280					285			
٠	290		-		-	295	Ala	_			300				
305		_			310	_	Asp		_	315					320
			-	325			Lys		330					335	
_			340		_		Arg	345					350		
		355					Thr 360					365			
	370					375	Gly				380				
385					390		Arg			395					400
	Ile	Cys	Arg	Leu 405	Glu	Glu	Gln	Leu	Gly 410	Arg	Met	GLU	Asn	Gly 415	Asp
Ala															

PCT/US00/05881 WO 00/55173

693

<211> 290 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (7) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (74) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (131) <223> Xaa equals any of the naturally occurring L-amino acids <400> 719 Glu Leu Ser Ala Ser Ala Xaa Asp Asp Gly Asn Phe Ser Leu Leu Ile Arg Ala Val Glu Glu Thr Asp Ala Gly Leu Tyr Thr Cys Asn Leu His 25 His His Tyr Cys His Leu Tyr Glu Ser Leu Ala Val Arg Leu Glu Val 40 Thr Asp Gly Pro Pro Ala Pro Pro Pro Thr Gly Thr Ala Arg Arg Arg 50 55 Cys Trp Arg Trp Arg Ala Ala Pro Ala Xaa Leu Thr Cys Val Asn Arg 70 Gly His Val Trp Thr Asp Arg His Val Glu Glu Ala Gln Gln Val Val 85 90 His Trp Asp Arg Gln Pro Pro Gly Val Pro His Asp Arg Ala Asp Arg 100 Leu Leu Asp Leu Tyr Ala Ser Ala Ser Ala Ala Leu Arg Ala Pro Phe 120 Ser Ala Xaa Arg Val Ala Val Gly Ala Asp Ala Phe Lys Arg Gly Asp 130 135 Phe Ser Leu Arg Ile Glu Pro Leu Glu Val Ala Asp Glu Gly Thr Tyr 150 Ser Cys His Leu His His His Tyr Trp Arg Ala Ala Thr Thr Ser Ser

165 170 175 Met Ser Ser Ser Pro Arg Ala Glu Pro Thr Ser Ser Ser Trp Ala 180 185 Thr Cys Trp Pro Arg Cys Cys Ser Ser Ser Cys Tyr Trp Ser Leu Ser 200 Ser Trp Pro Pro Ala Gly Arg Gly Gly Tyr Glu Tyr Ser Asp Gln Lys 215 Ser Gly Lys Ser Lys Gly Lys Asp Val Asn Leu Ala Glu Phe Ala Val 235 230 Ala Ala Gly Asp Gln Met Leu Tyr Arg Ser Glu Asp Ile Gln Leu Asp 250 Tyr Lys Asn Asn Ile Leu Lys Glu Arg Ala Glu Leu Ala His Ser Pro 265 Leu Pro Ala Lys Tyr Ile Asp Leu Asp Lys Gly Phe Arg Lys Glu Asn 280 Cys Lys 290 <210> 720 <211> 459 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (50) <223> Xaa equals any of the naturally occurring L-amino acids <400> 720 Asp Ala His Pro Lys Pro Cys Cys Glu Thr Ser Ala Ala Ala Cys Arg Leu Val Glu Arg Ile Leu Thr Ser Trp Glu Glu Asn Asp Arg Val Gln 20 25 Cys Ala Gly Gly Pro Arg Lys Gly Tyr Met Gly His Leu Thr Arg Val Ala Xaa Ala Leu Val Gln Asn Thr Glu Lys Gly Pro Asn Ala Glu Gln 50 55

Leu 65	Arg	Gln	Leu	Leu	Lys 70	Glu	Leu	Pro	Ser	Glu 75	Gln	Gln	Glu	Gln	Trp 80
Glu	Ala	Phe	Val	Ser 85	Gly	Pro	Leu	Ala	Glu 90	Thr	Asn	Lys	Lys	Asn 95	Met
Val	Asp	Leu	Val 100	Asn	Thr	His	His	Leu 105	His	Ser	Ser	Ser	Asp 110	Asp	Glu
Asp	Asp	Arg 115	Leu	Lys	Glu	Phe	Asn 120	Phe	Pro	Glu	Glu	Ala 125	Val	Leu	Gln
Gln	Ala 130	Phe	Met	Asp	Phe	Gln 135	Met	Gln	Arg	Met	Thr 140	Ser	Ala	Phe	Ile
Asp 145	His	Phe	Gly	Phe	Asn 150	Asp	Glu	Glu	Phe	Gly 155	Glu	Gln	Glu	Glu	Ser 160
Val	Asn	Ala	Pro	Phe 165	Asp	Lys	Thr	Ala	Asn 170	Ile	Thr	Phe	Ser	Leu 175	Asn
Ala	Asp	Asp	Glu 180	Asn	Pro	Asn	Ala	Asn 185	Leu	Leu	Glu	Ile	Cys 190	Tyr	Lys
Asp	Arg	Ile 195	Gln	Gln	Phe	Asp	Asp 200	Asp	Glu	Glu	Glu	Glu 205	Asp	Glu	Glu
Glu	Ala 210	Gln	Gly	Ser	Gly	Glu 215	Ser	Asp	Gly	Glu	Asp 220	Gly	Ala	Trp	Gln
Gly 225	Ser	Gln	Leu	Ala	Arg 230	Gly	Ala	Arg	Leu	Gly 235	Gln	Pro	Pro	Gly	Val 240
Arg	Ser	Gly	Gly	Ser 245	Thr	Asp	Ser	Glu	Asp 250	Glu	Glu	Glu	Glu	Asp 255	Glu
Glu	Glu	Glu	Glu 260	Asp	Glu	Glu	Gly	Ile 265	Gly	Cys	Ala	Ala	Arg 270	Gly	Gly
Ala	Thr	Pro 275	Leu	Ser	Tyr	Pro	Ser 280	Pro	Gly	Pro	Gln	Pro 285	Pro	Gly	Pro
Ser	Trp 290	Thr	Ala	Thr	Phe	Asp 295	Pro	Val	Pro	Thr	Asp 300	Ala	Pro	Thr	Ser
Pro 305	Arg	Val	Ser	Gly	Glu 310	Glu	Glu	Leu	His	Thr 315	Gly	Pro	Pro	Ala	Pro 320
Gln	Gly	Pro	Leu	Ser 325	Val	Pro	Gln	Gly	Leu 330	Pro	Thr	Gln	Ser	Leu 335	Ala

696

Ser Pro Pro Ala Arg Asp Ala Leu Gln Leu Arg Ser Gln Asp Pro Thr 340 345 Pro Pro Ser Ala Pro Gln Glu Ala Thr Glu Gly Ser Lys Val Thr Glu 360 Pro Ser Ala Pro Cys Gln Ala Leu Val Ser Ile Gly Asp Leu Gln Ala 375 380 Thr Phe His Gly Ile Arg Ser Ala Pro Ser Ser Ser Asp Ser Ala Thr 385 390 395 Arg Asp Pro Ser Thr Ser Val Pro Ala Ser Gly Ala His Gln Pro Pro 405 410 Gln Thr Thr Glu Gly Glu Lys Ser Pro Glu Pro Leu Gly Leu Pro Gln 425 Ser Gln Ser Ala Gln Ala Leu Thr Pro Pro Pro Ile Pro Asn Gly Ser 440 445 435 Ala Pro Glu Gly Pro Ala Ser Pro Gly Ser Gln 450 455 <210> 721 <211> 523

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Glu	Glu	Cys	Tyr 20	Met	Ala	Lys	Ile	Leu 25	Val	Ala	Glu	Gly	Thr 30	Arg	Asp
Val	Pro	Ile 35	Gly	Ala	Ile	Ile	Cys 40	Ile	Thr	Val	Gly	Lys 45	Pro	Glu	Asp
Ile	Glu 50	Ala	Phe	Lys	Asn	Tyr 55	Thr	Leu	Asp	Ser	Ser 60	Ala	Ala	Pro	Thr
Pro 65	Gln	Ala	Ala	Pro	Ala 70	Pro	Thr	Pro	Ala	Ala 75	Thr	Ala	Ser	Pro	Pro 80
Thr	Pro	Ser	Ala	Gln 85	Ala	Pro	Gly	Ser	Ser 90	Tyr	Pro	Pro	His	Met 95	Gln
Val	Leu	Leu	Pro 100	Ala	Leu	Ser	Pro	Thr 105	Met	Thr	Met	Gly	Thr 110	Val	Gln
Arg	Trp	Xaa 115	Lys	Lys	Val	Gly	Glu 120	Lys	Leu	Ser	Glu	Gly 125	Asp	Leu	Leu
	130					135					Phe 140				
145					150					155	Gly				160
		_		165		-			170		Lys			175	
			180					185			Thr		190		
		195					200				Ala	205			
	210					215					Cys 220				
225					230					235	Leu				240
				245					250		Lys			255	
Asp	Gly	Arg	11e 260		ГÀз	Lys		11e 265		Ser	Phe	Val	Pro 270	Ser	Lys

Val	Ala	Pro 275	Ala	Pro	Ala	Ala	Val 280	Val	Pro	Pro	Thr	Gly 285	Pro	Gly	Met
Ala	Pro 290	Val	Pro	Thr	Gly	Val 295	Phe	Thr	Asp	Ile	Pro 300	Ile	Ser	Asn	Ile
Arg 305	Arg	Val	Ile	Ala	Gln 310	Arg	Leu	Met	Gln	Ser 315	Lys	Gln	Thr	Ile	Pro 320
His	Tyr	Tyr	Leu	Ser 325	Ile	Xaa	Val	Asn	Met 330	Gly	Glu	Val	Leu	Leu 335	Val
Arg	Lys	Glu	Leu 340	Asn	Lys	Ile	Leu	Glu 345	Gly	Arg	Ser	Lys	Ile 350	Ser	Val
Asn	Asp	Phe 355	Ile	Ile	Lys	Ala	Ser 360	Ala	Leu	Ala	Cys	Leu 365	Lys	Val	Pro
Glu	Ala 370	Asn	Ser	Ser	Trp	Met 375	Asp	Thr	Val	Ile	Arg 380	Gln	Asn	His	Val
Val 385	Asp	Val	Ser	Val	Ala 390	Val	Ser	Thr	Pro	Ala 395	Gly	Leu	Ile	Thr	Pro 400
Ile	Val	Phe	Asn	Ala 405	His	Ile	Lys	Gly	Val 410	Glu	Thr	Ile	Ala	Asn 415	Asp
Val	Val	Ser	Leu 420	Ala	Thr	Lys	Ala	Arg 425	Glu	Gly	Lys	Leu	Gln 430	Pro	His
Glu	Phe	Gln 435	Gly	Gly	Thr	Phe	Thr 440	Ile	Ser	Asn	Leu	Gly 445	Met	Phe	Gly
Ile	Lys 450	Asn	Phe	Ser	Ala	Ile 455	Ile	Asn	Pro	Pro	Gln 460	Ala	Cys	Ile	Leu
Ala 465	Ile	Gly	Ala	Ser	Glu 470	Asp	Lys	Leu	Val	Pro 475	Ala	Asp	Asn	Glu	Lys 480
Gly	Phe	Asp	Val	Ala 485	Ser	Met	Met	Ser	Val 490	Thr	Leu	Ser	Суз	Asp 495	His
Arg	Val	Val	Asp 500	Gly	Ala	Val	Gly	Ala 505	Gln	Trp	Leu	Ala	Glu 510	Phe	Arg
Lys	Tyr	Leu 515	Glu	Lys	Pro	Ile	Thr 520	Met	Leu	Leu					

PCT/US00/05881

699

WO 00/55173

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<210> 722
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Asp Met Asn Asp Cys Tyr Ser Arg Leu Arg Arg Leu Val Pro Thr Ile
                                25
Pro Pro Asn Lys Lys Val Ser Lys Val Glu Ile Leu Gln His Val Ile
                            40
Asp Tyr Ile Leu Asp Leu Gln Leu Ala Leu Glu Thr His Pro Ala Leu
    50
                    55
Leu Arg Gln Pro Pro Pro Pro Ala Pro Pro His His Pro Ala Gly Thr
                    70
                                        75
Cys Pro Ala Ala Pro Pro Arg Thr Pro Leu Thr Ala Leu Asn Thr Asp
                          90
Pro Ala Gly Ala Val Asn Lys Gln Gly Asp Ser Ile Leu Cys Arg
                              105
           100
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<211> 190
<212> PRT
<213> Homo sapiens
Ser Gly Gly Gly Gly Arg Met Ile Lys Leu Phe Ser Leu Lys Gln
                5
                                   10
Gln Lys Lys Glu Glu Glu Ser Ala Gly Gly Thr Lys Gly Ser Ser Lys
                               25
Lys Ala Ser Ala Ala Gln Leu Arg Ile Gln Lys Asp Ile Asn Glu Leu
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40

55

Asn Leu Pro Lys Thr Cys Asp Ile Ser Phe Ser Asp Pro Asp Asp Leu

35

700

Leu Asn Phe Lys Leu Val Ile Cys Pro Asp Glu Gly Phe Tyr Lys Ser Gly Lys Phe Val Phe Ser Phe Lys Val Gly Gln Gly Tyr Pro His Asp 90 Pro Pro Lys Val Lys Cys Glu Thr Met Val Tyr His Pro Asn Ile Asp 100 Leu Glu Gly Asn Val Cys Leu Asn Ile Leu Arg Glu Asp Trp Lys Pro 120 Val Leu Thr Ile Asn Ser Ile Ile Tyr Gly Leu Gln Tyr Leu Phe Leu 130 135 Glu Pro Asn Pro Glu Asp Pro Leu Asn Lys Glu Ala Ala Glu Val Leu 150 155 145 Gln Asn Asn Arg Arg Leu Phe Glu Gln Asn Val Gln Arg Ser Met Arg 170 Gly Gly Tyr Ile Gly Ser Thr Tyr Phe Glu Arg Cys Leu Lys 180 185 <210> 724 <211> 524 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (247) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (417) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (440) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (443) <223> Xaa equals any of the naturally occurring L-amino acids

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Arg 1	Arg	Arg	Arg	Ala 5	Asp	Arg	Ala	Thr	Pro 10	Arg	Glu	Val	Leu	Glu 15	Thr
Pro	Gly	Ala	Ala 20	Ser	Val	Gln	Thr	Leu 25	Pro	Ser	Val	Thr	Met 30	Lys	Leu
Trp	Val	Ser 35	Ala	Leu	Leu	Met	Ala 40	Trp	Phe	Gly	Val	Leu 45	Ser	Cys	Val
Gln	Ala 50	Glu	Phe	Phe	Thr	Ser 55	Ile	Gly	His	Met	Thr 60	Asp	Leu	Ile	Tyr
Ala 65	Glu	Lys	Glu	Leu	Val 70	Gln	Ser	Leu	Lys	Glu 75	Tyr	Ile	Leu	Val	Glu 80
Glu	Ala	Lys	Leu	Ser 85	Lys	Ile	Lys	Ser	Trp 90	Ala	Asn	Lys	Met	Glu 95	Ala
Leu	Thr	Ser	Lys 100	Ser	Ala	Ala	Asp	Ala 105	Glu	Gly	Tyr	Leu	Ala 110	His	Pro
Val	Asn	Ala 115	Tyr	Lys	Leu	Val	Lys 120	Arg	Leu	Asn	Thr	Asp 125	Trp	Pro	Ala
Leu	Glu 130	Asp	Leu	Val	Leu	Gln 135	Asp	Ser	Ala	Ala	Gly 140	Phe	Ile	Ala	Asn
Leu 145	Ser	Val	Gln	Arg	Gln 150	Phe	Phe	Pro	Thr	Asp 155	Glu	Asp	Glu	Ile	Gly 160
Ala	Ala	Lys	Ala	Leu 165	Met	Arg	Leu	Gln	Asp 170	Thr	Tyr	Arg	Leu	Asp 175	Pro
Gly	Thr	Ile	Ser 180	Arg	Gly	Glu	Leu	Pro 185	Gly	Thr	Ļys	Tyr	Gln 190	Ala	Met
Leu	Ser	Val 195	Asp	Asp	Суз	Phe	Gly 200	Met	Gly	Arg	Ser	Ala 205	Туг	Asn	Glu
Gly	Asp 210	Tyr	Tyr	His	Thr	Val 215	Leu	Trp	Met	Glu	Gln 220	Val	Leu	Lys	Gln
Leu 225	Asp	Ala	Gly	Glu	Glu 230	Ala	Thr	Thr	Thr	Lys 235	Ser	Gln	Val	Leu	Asp 240
Tyr	Leu	Ser	туг	Ala 245	Val	Xaa	Gln	Leu	Gly 250	Asp	Leu	His	Arg	Ala 255	Leu
Glu	Leu	Thr	Ara	Ara	Leu	Leu	Ser	Leu	Asp	Pro	Ser	His	Glu	Arq	Ala

			260					265					270		
Gly	Gly	Asn 275	Leu	Arg	Tyr	Phe	Glu 280	Gln	Leu	Leu	Glu	Glu 285	Glu	Arg	Glu
Lys	Thr 290	Leu	Thr	Asn	Gln	Thr 295	Glu	Ala	Glu	Leu	Ala 300	Thr	Pro	Glu	Gly
11e 305	Tyr	Glu	Arg	Pro	Val 310	Asp	Tyr	Leu	Pro	Glu 315	Arg	Asp	Val	Tyr	Glu 320
Ser	Leu	Суѕ	Arg	Gly 325	Glu	Gly	Val	Lys	Leu 330	Thr	Pro	Arg	Arg	Gln 335	Lys
Arg	Leu	Phe	Cys 340	Arg	Tyr	His	His	Gly 345	Asn	Arg	Ala	Pro	Gln 350	Leu	Leu
Ile	Ala	Pro 355	Phe	Lys	Glu	Glu	Asp 360	Glu	Trp	Asp	Ser	Pro 365	His	Ile	Val
Arg	Tyr 370	Tyr	Asp	Val	Met	Ser 375	Asp	Glu	Glu	Ile	Glu 380	Arg	Ile	Lys	Glu
Ile 385	Ala	Lys	Pro	Lys	Leu 390	Ala	Arg	Ala	Thr	Val 395	Arg	Asp	Pro	Lys	Thr 400
Gly	Val	Leu	Thr	Val 405	Ala	Ser	туг	Arg	Val 410	Ser	Lys	Ser	Ser	Trp 415	Leu
Xaa	Glu	Asp	Asp 420	Asp	Pro	Val	Val	Ala 425	Arg	Val	Asn	Arg	Arg 430	Met	Gln
His	Ile	Thr 435	Gly	Leu	Thr	Val	Xaa 440	Thr	Ala	Xaa	Leu	Leu 445	Gln	Val	Ala
Asn	Туг 450	Gly	Val	Gly	Gly	Gln 455	Tyr	Glu	Pro	His	Phe 460	Asp	Phe	Ser	Arg
Asn 465	Asp	Glu	Arg	Asp	Thr 470	Phe	Lys	His	Leu	Gly 475	Thr	Gly	Asn	Arg	Val 480
Ala	Thr	Phe	Leu	Asn 485	Tyr	Met	Ser	Asp	Val 490	Glu	Ala	Gly	Gly	Ala 495	Thr
Val	Phe	Pro	Asp 500	Leu	Gly	Ala	Ala	Ile 505	Trp	Pro	Lys	Lys	Gly 510	Thr	Ala
Val	Phe	Trp 515	Tyr	Asn	Leu	Leu	Arg 520	Ser	Gly	Arg	Arg				

703

<210> 725 <211> 92 <212> PRT <213> Homo sapiens <400> 725 Leu Lys Met Thr Ser Leu Phe Ala Gln Glu Ile Arg Leu Ser Lys Arg 5 10. 15 His Glu Glu Ile Val Ser Gln Arg Leu Met Leu Leu Gln Gln Met Glu 25 Asn Lys Leu Gly Asp Gln His Thr Glu Lys Ala Ser Gln Leu Gln Thr 40 Val Glu Thr Ala Phe Lys Arg Asn Leu Ser Leu Leu Lys Asp Ile Glu 55 Ala Ala Glu Lys Ser Leu Gln Thr Arg Ile His Pro Leu Pro Arg Pro 70 Glu Val Val Ser Leu Glu Thr Arg Tyr Trp Ala Ser 90 <210> 726 <211> 690 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (108) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (123) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (383) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (688)

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<220> <221> SITE <222> (690) <223> Xaa equals any of the naturally occurring L-amino acids <400> 726 Val Ser Arg Ser Pro Arg Val Pro Leu Pro Pro Arg Ser Phe Ser Arg Met Ala Gly Asp Ser Thr Ala Thr Ser Arg Arg Leu Gly Ala Ala Pro Asp Arg Ala Ala Pro His Ile Leu Pro Ala Gly Ala His Arg Ala Ala Thr Ala Pro Gly Leu Gly Gly Gly Pro Glu Pro Leu Gly Arg Ala Leu 55 Ala Gly Gly Leu Arg Gly Pro Gln Gly Asn Gly Trp Leu Gln Glu Arg Lys Arg Arg Cys Pro Gly Leu Ala Gly Cys Phe Glu Ala Ile Ser Cys Gly Thr Gly Leu Gly Leu Pro Gly Leu Ala Leu Xaa Arg Glu Leu Ile Ser Trp Gly Ala Pro Gly Ser Ala Asp Ser Xaa Arg Leu Leu His Trp 120 Gly Ser His Pro Thr Ala Phe Val Val Ser Tyr Ala Ala Ala Leu Pro 135 130 Ala Ala Leu Trp His Lys Leu Gly Ser Leu Trp Val Pro Gly Gly 150 155 Gln Gly Gly Ser Gly Asn Pro Val Arg Arg Leu Leu Gly Cys Leu Gly 170 Ser Glu Thr Arg Arg Leu Ser Leu Phe Leu Val Leu Val Leu Ser 185 180 Ser Leu Gly Glu Met Ala Ile Pro Phe Phe Thr Gly Arg Leu Thr Asp 200 Trp Ile Leu Gln Asp Gly Ser Ala Asp Thr Phe Thr Arg Asn Leu Thr

215

230

Leu Met Ser Ile Leu Thr Ile Ala Ser Ala Val Leu Glu Phe Val Gly

220

235

210

Asp Gly Ile Tyr Asn Asn Thr Met Gly His Val His Ser His Leu Gln Gly Glu Val Phe Gly Ala Val Leu Arg Gln Glu Thr Glu Phe Phe Gln Gln Asn Gln Thr Gly Asn Ile Met Ser Arg Val Thr Glu Asp Thr Ser 280 Thr Leu Ser Asp Ser Leu Ser Glu Asn Leu Ser Leu Phe Leu Trp Tyr 295 Leu Val Arg Gly Leu Cys Leu Leu Gly Ile Met Leu Trp Gly Ser Val Ser Leu Thr Met Val Thr Leu Ile Thr Leu Pro Leu Leu Phe Leu Leu 325 Pro Lys Lys Val Gly Lys Trp Tyr Gln Leu Leu Glu Val Gln Val Arg 345 Glu Ser Leu Ala Lys Ser Ser Gln Val Ala Ile Glu Ala Leu Ser Ala Met Pro Thr Val Arg Ser Phe Ala Asn Glu Glu Glu Glu Ala Xaa Lys 375 Phe Arg Glu Lys Leu Gln Glu Ile Lys Thr Leu Asn Gln Lys Glu Ala 395 Val Ala Tyr Ala Val Asn Ser Trp Thr Thr Ser Ile Ser Gly Met Leu 405 Leu Lys Val Gly Ile Leu Tyr Ile Gly Gly Gln Leu Val Thr Ser Gly Ala Val Ser Ser Gly Asn Leu Val Thr Phe Val Leu Tyr Gln Met Gln Phe Thr Gln Ala Val Glu Val Leu Leu Ser Ile Tyr Pro Arg Val Gln 455 Lys Ala Val Gly Ser Ser Glu Lys Ile Phe Glu Tyr Leu Asp Arg Thr 470 475 Pro Arg Cys Pro Pro Ser Gly Leu Leu Thr Pro Leu His Leu Glu Gly 490 Leu Val Gln Phe Gln Asp Val Ser Phe Ala Tyr Pro Asn Arg Pro Asp

505

Val Leu Val Leu Gln Gly Leu Thr Phe Thr Leu Arg Pro Gly Glu Val 520 Thr Ala Leu Val Gly Pro Asn Gly Ser Gly Lys Ser Thr Val Ala Ala 535 Leu Leu Gln Asn Leu Tyr Gln Pro Thr Gly Gly Gln Leu Leu Leu Asp 550 Gly Lys Pro Leu Pro Gln Tyr Glu His Arg Tyr Leu His Arg Gln Val 570 Ala Ala Val Gly Gln Glu Pro Gln Val Phe Gly Arg Ser Leu Gln Glu Asn Ile Ala Tyr Gly Leu Thr Gln Lys Pro Thr Met Glu Glu Ile Thr Ala Ala Val Lys Ser Gly Ala His Ser Phe Ile Ser Gly Leu Pro 615 Gln Gly Tyr Asp Thr Glu Val Asp Glu Ala Gly Ser Gln Leu Ser Gly 635 Gly Gln Arg Gln Ala Val Ala Leu Ala Arg Ala Leu Ile Arg Lys Pro Cys Val Leu Ile Leu Asp Asp Ala Thr Ser Ala Leu Asp Ala Asn Ser 665 Gln Leu Gln Val Glu Gln Leu Leu Tyr Glu Ser Pro Glu Arg Tyr Xaa 680 Arg Xaa 690 <210> 727 <211> 82 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (44) <223> Xaa equals any of the naturally occurring L-amino acids <220>

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Thr Asn Pro Ile Val Asn Ser Ala Cys Lys Gly Ser Arg Leu Cys Ala
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Pro Tyr Glu Asn Leu Met Pro Asp Asp Leu Arg Xaa Asn Ser Phe Ile
Leu Lys Pro Pro Phe Thr Leu Gln Ser Val Glu Lys Leu Ser Ser Thr
     50
Lys Leu Val Pro Gly Ala Lys Asn Xaa Gly Asp Arg Cys Ser Arg Glu
Arg Ser
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<400)> 7	28													
Ser 1	Arg	Val	Lys	Pro 5	Arg	Val	Arg	Gly	Thr 10	Xaa	Val	Arg	Thr	Pro 15	Gly
Ser	Arg	Arg	Gly 20	Arg	His	Gly	Ala	Val 25	Pro	Gly	Asp	Trp	Glu 30	Ala	Ala
Ala	Gln	Ala 35	Arg	Gly	Ala	Gly	Gln 40	Arg	Leu	Pro	Thr	Pro 45	Ser	Glu	Ile
Leu	Ser 50	Asn	Ala	Gly	Leu	Arg 55	Phe	Glu	Val	Val	Pro 60	Ser	Lys	Phe	Lys
Glu 65	Lys	Leu	Asp	Lys	Ala 70	Ser	Phe	Ala	Thr	Pro 75	Tyr	Gly	туг	Ala	Met 80
Glu	Thr	Ala	Lys	Gln 85	Lys	Ala	Leu	Glu	Val 90	Ala	Asn	Arg	Leu	Туг 95	Gln
Lys	Asp	Leu	Arg 100	Ala	Pro	Asp	Val	Val 105	Ile	Gly	Ala	Asp	Thr 110	Ile	Val
Thr	Val	Gly 115	Gly	Leu	Ile	Leu	Glu 120	Lys	Pro	Val	Asp	Lys 125	Gln	Asp	Ala
Tyr	Arg 130	Met	Leu	Ser	Arg	Leu 135	Ser	Gly	Arg	Glu	His 140	Ser	Val	Phe	Thr
Gly 145	Val	Ala	Ile	Val	His 150	Cys	Ser	Ser	Lys	Asp 155	His	Gln	Leu	Asp	Thr 160
Arg	Val	Ser	Glu	Phe 165	Tyr	Glu	Glu	Thr	Lys 170	Val	Lys	Phe	Ser	Glu 175	Leu
Ser	Glu	Glu	Leu 180	Leu	Trp	Glu	Tyr	Val 185	His	Ser	Gly	Glu	Pro 190	Met	Asp
Lys	Ala	Gly 195	Gly	Tyr	Gly	Ile	Gln 200	Ala	Leu	Gly	Gly	Met 205	Leu	Val	Glu
Ser	Val 210	His	Gly	Asp	Phe	Leu 215	Asn	Val	Val	Gly	Phe 220	Pro	Leu	Asn	His
Phe 225	Cys	Lys	Gln	Leu	Val 230	Lys	Leu	Tyr	Tyr	Pro 235	Pro	Arg	Pro	Glu	Asp 240
Leu	Arg	Arg	Ser	Val		His	Asp		Ile	Pro	Ala	Ala		Thr 255	

WO 00/55173

Glu	Asp	Leu	Ser 260	Asp	Val	Glu	Gly	Gly 265	Gly	Ser	Glu	Pro	Thr 270	Gln	Arg
Asp	Ala	Gly 275	Ser	Arg	Asp	Glu	Lys 280	Ala	Glu	Ala	Gly	Glu 285	Ala	Gly	Gln
Ala	Thr 290	Ala	Glu	Ala	Glu	Cys 295	His	Arg	Thr	Arg	Glu 300	Thr	Leu	Pro	Pro
Phe 305		Thr	Arg	Leu	Leu 310	Glu	Leu	Ile	Glu	Gly 315	Phe	Met	Leu	Ser	Lys 320
Gly	Leu	Leu	Thr	Ala 325	Суз	Lys	Leu	Lys	Val 330	Phe	Asp	Leu	Leu	Lys 335	Asp
Glu	Ala	Pro	Gln 340	Lys	Ala	Ala	Asp	11e 345	Ala	Ser	Lys	Val	Asp 350	Ala	Ser
Ala	Cys	Gly 355	Met	Glu	Arg	Leu	160 360	Asp	Ile	Cys	Ala	Ala 365	Met	Gly	Leu
	370					375	Tyr				380				
385				-	390		Tyr			395	-				400
		_		405	-		Leu		410	-				415	
			420				His	425					430		
		435				_	Tyr 440					445			
	450					455	Met		_		460		_		
465					470		Arg			475					480
			-	485			Arg		490					495	
			500				Leu	505					510		
HIS	Phe	Gln 515	Pro	Pro	GIA	rro	Gln 520	GIn	cys	Arg	ser	Thr 525	ser	GIN	GIN

Val Thr Phe Ser Gly Thr Pro Ser Pro Ala Leu Ser Cys Thr Ser Cys 535 Ala Gly Ser Cys Met Xaa Gly Gln Thr Thr Lys Ser Thr Ser Tyr Ser 550 555 Ala Gly Ser Pro Arg Ala Ala Ser Gln Gly Pro Ala Cys Cys Trp Trp 570 565 Arg Arg Ser Trp Met Arg Arg Gly Trp Arg Xaa Arg Xaa Asp Ala 585 Val Thr Glu His Ala Gly Ala Asp 595 <210> 729 <211> 535 <212> PRT <213> Homo sapiens <400> 729 Gly Arg Ser Ser Phe Thr Ser Leu Val Val Gly Val Phe Val Val Tyr 10

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Cys Ser Gly Asp Ala Asn Cys Ile Gln Pro Tyr Leu Ala Arg Arg Pro 35 40 45

Lys Leu Gln Leu Ser Val Tyr Thr Thr Thr Arg Ser His Leu Gly Ala
50 60

Glu Asn Asn Ile Asp Leu Val Leu Asn Val Glu Asp Phe Asp Val Glu
65 70 75 80

Ser Lys Phe Glu Arg Thr Val Asn Val Ser Val Pro Lys Lys Thr Arg 85 90 95

Asn Asn Gly Thr Leu Tyr Ala Tyr Ile Phe Leu His His Ala Gly Val 100 105 110

Leu Pro Trp His Asp Gly Lys Gln Val His Leu Val Ser Pro Leu Thr
115 120 125

Thr Tyr Met Val Pro Lys Pro Glu Glu Ile Asn Leu Leu Thr Gly Glu 130 135 140

145	Asp	Tnr	GIN	GIn	11e 150	GIU	Ala	GIU	гуз	155	PIO	Thr	ser	Ald	160
Asp	Glu	Pro	Val	Ser 165	His	Trp	Arg	Pro	Arg 170	Leu	Ala	Leu	Asn	Val 175	Met
Ala	Asp	Asn	Phe 180	Val	Phe	Asp	Gly	Ser 185	Ser	Leu	Pro	Ala	Asp 190	Val	His
Arg	Tyr	Met 195	Lys	Met	Ile	Gln	Leu 200	Gly	Lys	Thr	Val	His 205	Tyr	Leu	Pro
Ile	Leu 210	Phe	Ile	Asp	Gln	Leu 215	Ser	Asn	Arg	Val	Lys 220	Asp	Leu	Met	Val
Ile 225	Asn	Arg	Ser	Thr	Thr 230	Glu	Leu	Pro	Leu	Thr 235	Val	Ser	Tyr	Asp	Lys 240
Val	Ser	Leu	Gly	Arg 245	Leu	Arg	Phe	Trp	Ile 250	His	Met	Gln	Asp	Ala 255	Val
Tyr	Ser	Leu	Gln 260	Gln	Phe	Gly	Phe	Ser 265	Glu	Lys	Asp	Ala	Asp 270	Glu	Val
	_	275					280				Leu	285			
	290					295		•			Leu 300				
Asp 305	Ile	Ser	Phe	Trp	Lys 310	Lys	Lys	Lys	Ser	Met 315	Ile	Gly	Met	Ser	Thr 320
-				325		_			330		Val			335	
		_	340					345			Val		350		
		355					360		•		Ala	365			
	370	_	-	-	•	375					Phe 380				
385					390					395	Gln				400
Leu	Ser	Tyr	Leu	Leu 405	Tyr	Pro	Leu	Cys	Val 410	Gly	Gly	Ala	Val	Tyr 415	Ser

Leu Leu Asn Ile Lys Tyr Lys Ser Trp Tyr Ser Trp Leu Ile Asn Ser 425 420

Phe Val Asn Gly Val Tyr Ala Phe Gly Phe Leu Phe Met Leu Pro Gln 440

Leu Phe Val Asn Tyr Lys Leu Lys Ser Val Ala His Leu Pro Trp Lys 455

Ala Phe Thr Tyr Lys Ala Phe Asn Thr Phe Ile Asp Asp Val Phe Ala 470 475

Phe Ile Ile Thr Met Pro Thr Ser His Arg Leu Ala Cys Phe Arg Asp 490

Asp Val Val Phe Leu Val Tyr Leu Tyr Gln Arg Trp Leu Tyr Pro Val 505

Asp Lys Arg Arg Val Asn Glu Phe Gly Glu Ser Tyr Glu Glu Lys Ala 525 515 520

Thr Arg Ala Pro His Thr Asp 530

<210> 730

<211> 288

<212> PRT

<213> Homo sapiens

<400> 730

Arg Pro Ala Gly Val Thr Glu Leu Gln Pro Arg Ala Pro Gly Gly Gly

Gly Met Glu Ala Ala Ala Glu Pro Gly Asn Leu Ala Gly Val Arg His 20 25

Ile Ile Leu Val Leu Ser Gly Lys Gly Gly Val Gly Lys Ser Thr Ile

Ser Thr Glu Leu Ala Leu Ala Leu Arg His Ala Gly Lys Lys Val Gly 55

Ile Leu Asp Val Asp Leu Cys Gly Pro Ser Ile Pro Arg Met Leu Gly 70

Ala Gln Gly Arg Ala Val His Gln Cys Asp Arg Gly Trp Ala Pro Val 90

Phe Leu Asp Arg Glu Gln Ser Ile Ser Leu Met Ser Val Gly Phe Leu

713

105 110 100 Leu Glu Lys Pro Asp Glu Ala Val Val Trp Arg Gly Pro Lys Lys Asn 115 120 Ala Leu Ile Lys Gln Phe Val Ser Asp Val Ala Trp Gly Glu Leu Asp 135 Tyr Leu Val Val Asp Thr Pro Pro Gly Thr Ser Asp Glu His Met Ala 155 Thr Ile Glu Ala Leu Arg Pro Tyr Gln Pro Leu Gly Ala Leu Val Val 165 170 Thr Thr Pro Gln Ala Val Ser Val Gly Asp Val Arg Arg Glu Leu Thr 185 Phe Cys Arg Lys Thr Gly Leu Arg Val Met Gly Ile Val Glu Asn Met 200 Ser Gly Phe Thr Cys Pro His Cys Thr Glu Cys Thr Ser Val Phe Ser Arg Gly Gly Glu Glu Leu Ala Gln Leu Ala Gly Val Pro Phe Leu Gly Ser Val Pro Leu Asp Pro Ala Leu Met Arg Thr Leu Glu Glu Gly 250 His Asp Phe Ile Gln Glu Phe Pro Gly Ser Pro Ala Phe Ala Ala Leu 260 Thr Ser Ile Ala Gln Lys Ile Leu Asp Ala Thr Pro Ala Cys Leu Pro 280

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Asp Gln Leu Cys Gly Pro Gln Thr Tyr Lys Glu His Leu Glu Gly Gln 1 5 10 15

Lys His Lys Lys Clu Ala Ala Leu Lys Ala Ser Gln Asn Thr Ser 20 25 30

PCT/US00/05881

Ser	Ser	Asn 35	Ser	Ser	Thr	Arg	Gly 40	Thr	Gln	Asn	Gln	Leu 45	Arg	Cys	Glu
Leu	Cys 50	Asp	Val	Ser	Суз	Thr 55	Gly	Ala	Asp	Ala	Tyr 60	Ala	Ala	His	Ile
Arg 65	Gly	Ala	Lys	His	Gln 70	Lys	Val	Val	Lys	Leu 75	His	Thr	Lys	Leu	Gly 80
ГÀа	Pro	Ile	Pro	Ser 85	Thr	Glu	Pro	Asn	Val 90	Val	Ser	Gln	Ala	Thr 95	Ser
Ser	Thr	Ala	Val 100	Ser	Ala	Ser	Lys	Pro 105	Thr	Ala	Ser	Pro	Ser 110	Ser	Ile
Ala	Ala	Asn 115	Asn	Cys	Thr	Val	Asn 120	Thr	Ser	Ser	Ile	Ala 125	Thr	Ser	Ser
	130	Gly				135	_				140				
Asn 145	Thr	Lys	Val	Ser	Ala 150	Val	Pro	Thr	Asn	Met 155	Ala	Ala	Lys	Lys	Thr 160
		Pro		165				_	170				•	175	
_		Lys	180		-			185			_		190		
		Thr 195					200				_	205			
	210	Pro				215					220				
225		Val			230					235					240
-		Ile	-	245		•	-		250		-			255	_
		Ala	260					265	_				270	*	
		Lys 275					280					285			
īīe	Arg 290	Ala	Arg	гЛs	IIE	Gln 295	GIU	GIU	rys	Met	Arg 300	гÀг	GIN	Met	Gln

Lys 305	Glu	Glu	Tyr	Trp	Arg 310	Arg	Arg	Glu	Glu	Glu 315	Glu	Arg	Trp	Arg	Met 320
Glu	Met	Arg	Arg	Tyr 325	Glu	Glu	Asp	Met	Tyr 330	Trp	Arg	Arg	Met	Glu 335	Glu
Glu	Gln	His	His 340	Trp	Asp	Asp	Arg	Arg 345	Arg	Met	Pro	Asp	Gly 350	Gly	Tyr
Pro	His	Gly 355	Pro	Pro	Gly	Pro	Leu 360	Gly	Leu	Leu	Gly	Val 365	Arg	Pro	Gly
Met	Pro 370	Pro	Gln	Pro	Gln	Gly 375	Pro	Ala	Pro	Leu	Arg 380	Arg	Pro	Asp	Ser
Ser 385	_	Asp	Arg	Tyr	Val 390	Met	Thr	Lys	His	Ala 395	Thr	Ile	Tyr	Pro	Thr 400
Glu	Glu	Glu	Leu	Gln 405	Ala	Val	Gln	Lys	11e 410	Val	Ser	Ile	Thr	Glu 415	Arg
Ala	Leu	Lys	Leu 420	Val	Ser	Asp	Ser	Leu 425	Ser	Glu	His	Glu	Lys 430	Asn	Lys
		435			Asp		440				_	445			
	450				Val	455					460				
465					Asn 470					475					480
				485	Arg				490					495	
			500		Lys			505		_			510		
		515			Ser		520					525			
	530				Ile	535	_				540				
545					Val 550	-				555					560
Lys	Суз	Leu	Asp	Ala 565	Leu	Ala	Ala		Arg 570	His	Ala	Lys	Trp	Phe 575	Gln

Ala Arg Ala Asn Gly Leu Gln Ser Cys Val Ile Ile Ile Arg Ile Leu Arg Asp Leu Cys Gln Arg Val Pro Thr Trp Ser Asp Phe Pro Ser Trp 600 Ala Met Glu Leu Leu Val Glu Lys Ala Ile Ser Ser Ala Ser Ser Pro 615 Gln Ser Pro Gly Asp Ala Leu Arg Arg Val Phe Glu Cys Ile Ser Ser 630 635 Gly Ile Ile Leu Lys Gly Ser Pro Gly Leu Leu Asp Pro Cys Glu Lys Asp Pro Phe Asp Thr Leu Ala Thr Met Thr Asp Gln Gln Arg Glu Asp 665 Ile Thr Ser Ser Ala Gln Phe Ala Leu Arg Leu Leu Ala Phe Arg Gln 680 Ile His Lys Val Leu Gly Met Asp Pro Leu Pro Gln Met Ser Gln Arg 690 695

Phe Asn Ile His Asn Asn Arg Lys Arg Arg Arg Asp Ser Asp Gly Val 705 715

Asp Gly Phe Glu Ala Glu Gly Lys Lys Asp Lys Lys Asp Tyr Asp Asn 730 725

Phe

<210> 732

<211> 106

<212> PRT

<213> Homo sapiens

Gly Arg Gly Leu Asn Ser Pro Lys Glu Leu Arg Pro Leu Thr Arg Ala

Ala Pro Ala Ala Ala Cys Thr Gly Pro Gly Ala Ala Met Pro Lys

Cys Pro Lys Cys Asn Lys Glu Val Tyr Phe Ala Glu Arg Val Thr Ser 35 40

Leu Gly Lys Asp Trp His Arg Pro Cys Leu Lys Cys Glu Lys Cys Gly 50

Lys Thr Leu Thr Ser Gly Gly His Ala Glu His Glu Gly Lys Pro Tyr 70

Cys Asn His Pro Cys Tyr Ala Ala Met Phe Gly Pro Lys Gly Phe Gly 90

Arg Gly Gly Ala Glu Ser His Thr Phe Lys 100 105

<210> 733

<211> 230

<212> PRT

<213> Homo sapiens

<400> 733

Ala Ser Cys Leu Gln Ser Val Ala Ser Ala Cys Ala Ser Phe Pro Ala

Pro Ser Trp Arg Gly Thr Arg Lys Arg Asn Ala Thr Asp Arg Val Thr 25

Gln Cys Lys Tyr Lys Arg Ile Gly Cys Pro Trp His Gly Pro Phe His 40

Glu Leu Thr Val His Glu Ala Ala Cys Ala His Pro Thr Lys Thr Gly 50

Ser Glu Leu Met Glu Ile Leu Asp Gly Met Asp Gln Ser His Arg Lys

Glu Met Gln Leu Tyr Asn Ser Ile Phe Ser Leu Leu Ser Phe Glu Lys 90

Ile Gly Tyr Thr Glu Val Gln Phe Arg Pro Tyr Arg Thr Asp Asp Phe 100 105

Ile Thr Arg Leu Tyr Tyr Glu Thr Pro Arg Phe Thr Val Leu Asn Gln 120

Thr Trp Val Leu Lys Ala Arg Val Asn Asp Ser Glu Arg Asn Pro Asn 130 135

Leu Ser Cys Lys Arg Thr Leu Ser Phe Gln Leu Leu Lys Ser Lys 145 155

Val Thr Ala Pro Leu Glu Cys Ser Phe Leu Leu Lys Gly Pro Tyr

718

170 175 165 Asp Asp Val Arg Ile Ser Pro Val Ile Tyr His Phe Val Phe Thr Asn 185 180 Glu Ser Asn Glu Thr Asp Tyr Val Pro Leu Pro Ile Ile Asp Ser Val 200 Glu Cys Asn Lys Leu Leu Ala Ala Lys Asn Ile Asn Leu Arg Leu Phe 215 220 Leu Phe Gln Ile Gln Lys 225 230 <210> 734 <211> 222 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (18) <223> Xaa equals any of the naturally occurring L-amino acids Gly Arg Pro Ala Pro Pro Ala Ala Arg Ala Gly Ala His Ser Arg Gly 10 Ala Xaa Ala Pro Pro Ala Ala Ile Asp Met Met Phe Pro Gln Ser Arg 25 His Ser Gly Ser Ser His Leu Pro Gln Gln Leu Lys Phe Thr Thr Ser 35 Asp Ser Cys Asp Arg Ile Lys Asp Glu Phe Gln Leu Leu Gln Ala Gln Tyr His Ser Leu Lys Leu Glu Cys Asp Lys Leu Ala Ser Glu Lys Ser 75 Glu Met Gln Arg. His Tyr Val Met Tyr Tyr Glu Met Ser Tyr Gly Leu Asn Ile Glu Met His Lys Gln Ala Glu Ile Val Lys Arg Leu Asn Gly 105 Ile Cys Ala Gln Val Leu Pro Tyr Leu Ser Gln Glu His Gln Gln Gln

Val Leu Gly Ala Ile Glu Arg Ala Lys Gln Val Thr Ala Pro Glu Leu 130 135 Asn Ser Ile Ile Arg Gln Gln Leu Gln Ala His Gln Leu Ser Gln Leu 150 155 Gln Ala Leu Ala Leu Pro Leu Thr Pro Leu Pro Val Gly Leu Gln Pro 170 165 Pro Ser Leu Pro Ala Val Ser Ala Gly Thr Gly Leu Leu Ser Leu Ser 180 185 Ala Leu Gly Ser Gln Ala His Leu Ser Lys Glu Asp Lys Asn Gly His 200 Asp Gly Asp Thr His Gln Glu Asp Asp Gly Glu Lys Ser Asp 215 <210> 735 <211> 248 <212> PRT <213> Homo sapiens <400> 735 Gly Thr Ser Asp Met Glu Leu Phe Leu Ala Gly Arg Arg Val Leu Val Thr Gly Ala Gly Lys Gly Ile Gly Arg Gly Thr Val Gln Ala Leu His 20 Ala Thr Gly Ala Arg Val Val Ala Val Ser Arg Thr Gln Ala Asp Leu Asp Ser Leu Val Arg Glu Cys Pro Gly Ile Glu Pro Val Cys Val Asp 55 Leu Gly Asp Trp Glu Ala Thr Glu Arg Ala Leu Gly Ser Val Gly Pro Val Asp Leu Leu Val Asn Asn Ala Ala Val Ala Leu Leu Gln Pro Phe 90 Leu Glu Val Thr Lys Glu Ala Phe Asp Arg Ser Phe Glu Val Asn Leu 100 105 Arg Ala Val Ile Gln Val Ser Gln Ile Val Ala Arg Gly Leu Ile Ala 115 120

Arg Gly Val Pro Gly Ala Ile Val Asn Val Ser Ser Gln Cys Ser Gln

720

140

135

130

Arg Ala Val Thr Asn His Ser Val Tyr Cys Ser Thr Lys Gly Ala Leu 150 Asp Met Leu Thr Lys Val Met Ala Leu Glu Leu Gly Pro His Lys Ile 170 165 Arg Val Asn Ala Val Asn Pro Thr Val Val Met Thr Ser Met Gly Gln 185 Ala Thr Trp Ser Asp Pro His Lys Ala Lys Thr Met Leu Asn Arg Ile 195 200 Pro Leu Gly Lys Phe Ala Glu Val Glu His Val Val Asn Ala Ile Leu 215 Phe Leu Leu Ser Asp Arg Ser Gly Met Thr Thr Gly Ser Thr Leu Pro 235 Val Glu Gly Gly Phe Trp Ala Cys 245 <210> 736 <211> 216 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (61) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (68) <223> Xaa equals any of the naturally occurring L-amino acids <400> 736 Arg Leu Leu Phe Arg Val Arg Lys Arg Met Ile Ser Phe Ser Ala Pro 10 Pro Leu Met Leu Pro Phe Ser Phe Tyr Phe Phe Val Phe Pro Val Ala 20 Arg Thr Ala Arg Lys Arg Lys Pro Ser Pro Glu Pro Glu Gly Glu Val

Gly Pro Pro Lys Ile Asn Gly Glu Ala Gln Pro Trp Xaa Ser Thr Ser

721

60

55

Thr Glu Gly Xaa Lys Ile Pro Met Thr Pro Thr Ser Ser Phe Val Ser 70 75 Pro Pro Pro Pro Thr Ala Ser Pro His Ser Asn Arg Thr Thr Pro Pro 90 Glu Ala Ala Gln Asn Gly Gln Ser Pro Met Ala Ala Leu Ile Leu Val 105 Ala Asp Asn Ala Gly Gly Ser His Ala Ser Lys Asp Ala Asn Gln Val 120 His Ser Thr Thr Arg Arg Asn Ser Asn Ser Pro Pro Ser Pro Ser Ser 135 Met Asn Gln Arg Arg Leu Gly Pro Arg Glu Val Gly Gln Gly Ala 150 155 Gly Asn Thr Gly Gly Leu Glu Pro Val His Pro Ala Ser Leu Pro Asp 165 170 Phe Ser Leu Ala Thr Ser Ala Pro Leu Cys Cys Thr Leu Cys His Glu 180 185 Arg Leu Glu Asp Asn His Phe Val Gln Cys Arg Pro Ser Phe Asp Lys 200 Phe Ser Ser Leu Leu Arg Gln Arg 210 215 <210> 737 <211> 317 <212> PRT <213> Homo sapiens <400> 737 Arg Pro Thr Arg Pro Glu Val Met Met Thr Lys Tyr Ser Asn Leu Ser Leu Glu Ser His Asn Phe Ser Leu Thr Ala Ser Pro Leu Thr Ser Leu Pro Ile Pro Glu Val Met Met Thr Lys Tyr Ser Asn Leu Phe Leu Glu 35 40 Ser His Asn Ile Ser Leu Thr Glu His Ser Ser Val Pro Val Glu Lys

65	116	1111	neu	GIU	70	rio	Der	nia	Vai	75	neu	****	Cys	01	80
Thr	Thr	Ser	Gly	Asp 85	Val	Asn	Ser	Val	Asn 90	Val	Thr	Trp	Lys	Lys 95	Gly
Asp	Glu	Gln	Leu 100	Lys	Asn	Tyr	His	Val 105	Ser	Ala	Thr	Glu	Gly 110	Ile	Leu
Tyr	Thr	Gln 115	Tyr	Lys	Phe	Ser	Ile 120	Ile	Asn	Ser	Glu	Gln 125	Leu	Gly	Ser
туг	Ser 130	Cys	Phe	Phe	Glu	Glu 135	Glu	Lys	Glu	Arg	Arg 140	Gly	Thr	Phe	Asn
Phe 145	Gly	Val	Pro	Glu	Val 150	Gln	Arg	Lys	Asn	Lys 155	Pro	Leu	Ile	Thr	Туг 160
		-	Ser	165				-	170				-	175	•
			Thr 180					185					190		
Asp	Val	His 195	Met	Asn	Glu	Lys	Tyr 200	Ala	Ile	Asn	Gly	Thr 205	Asn	Ala	Asn
	210		Leu			215					220				
225	_	_	His		230				-	235					240
			Val	245		_			250		-			255	
			Glu 260					265					270	_	
		275	Gln	-	-	-	280			_	-	285	-		
	290		Glu			295					300		116	GIU	ASN
Asn 305			Arg		-	-						GIU			

PCT/US00/05881

<210> 738 <211> 67 <212> PRT

<213> Homo sapiens

<400> 738

Ala Arg Val Ala Ser Asp Pro Phe Phe Arg His Tyr Arg Gln Leu Asn
1 5 10 15

Glu Lys Leu Val Gln Leu Ile Glu Asp Tyr Ser Leu Val Ser Phe Ile 20 25 30

Pro Leu Asn Ile Gln Asp Lys Glu Ser Ile Gln Arg Val Leu Gln Ala 35 40 45

Val Asp Lys Ala Asn Gly Tyr Cys Phe Gly Ala Gln Glu Gln Arg Thr 50 55 60

Trp Lys Pro 65

<210> 739

<211> 142

<212> PRT

<213> Homo sapiens

<400> 739

Ser Gln Gln Pro Arg Ile Met Ser Lys Leu Gly Arg Ala Ala Arg Gly
1 5 10 15

Leu Arg Lys Pro Glu Val Gly Gly Val Ile Arg Ala Ile Val Arg Ala 20 25 30

Gly Leu Ala Met Pro Gly Pro Pro Leu Gly Pro Val Leu Gly Gln Arg
35 40 45

Gly Val Ser Ile Asn Gln Phe Cys Lys Glu Phe Asn Glu Arg Thr Lys
50 60

Asp Ile Lys Glu Gly Ile Pro Leu Pro Thr Lys Ile Leu Val Lys Pro 65 70 75 80

Asp Arg Thr Phe Glu Ile Lys Ile Gly Gln Pro Thr Val Ser Tyr Phe

Leu Lys Ala Ala Ala Gly Ile Glu Lys Gly Ala Arg Gln Thr Gly Lys
100 105 110

Glu Val Ala Gly Leu Val Thr Leu Lys His Val Tyr Glu Ile Ala Arg

724

120 125 115 Ile Lys Ala Gln Asp Glu Ala Phe Ala Cys Arg Met Tyr Pro 135 130 <210> 740 <211> 485 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (12) <223> Xaa equals any of the naturally occurring L-amino acids Trp Pro Ala Val Ala Val Arg Phe Thr Ala Leu Xaa Leu Gly Phe Gly 10 Asp Ala Val His Val Tyr Asp Gly Pro Gly Pro Pro Glu Ser Ser Arg Leu Leu Arg Ser Leu Thr His Phe Ser Asn Gly Lys Ala Val Thr Val 35 40 Glu Thr Leu Ser Gly Gln Ala Val Val Ser Tyr His Thr Val Ala Trp Ser Asn Gly Arg Gly Phe Asn Ala Thr Tyr His Val Arg Gly Tyr Cys Leu Pro Trp Asp Arg Pro Cys Gly Leu Gly Ser Gly Leu Gly Ala Gly Glu Gly Leu Gly Glu Arg Cys Tyr Ser Glu Ala Gln Arg Cys Asp Gly 105 Ser Trp Asp Cys Ala Asp Gly Thr Asp Glu Glu Asp Cys Pro Gly Cys 120 Pro Pro Gly His Phe Pro Cys Gly Ala Ala Gly Thr Ser Gly Ala Thr 130 135 Ala Cys Tyr Leu Pro Ala Asp Arg Cys Asn Tyr Gln Thr Phe Cys Ala

Asp Gly Ala Asp Glu Arg Arg Cys Arg His Cys Gln Pro Gly Asn Phe

170 .

PCT/US00/05881 WO 00/55173

725

Arg Cys Arg Asp Glu Lys Cys Val Tyr Glu Thr Trp Val Cys Asp Gly 180 185 Gln Pro Asp Cys Ala Asp Gly Ser Asp Glu Trp Asp Cys Ser Tyr Val Leu Pro Arg Lys Val Ile Thr Ala Ala Val Ile Gly Ser Leu Val Cys 215 Gly Leu Leu Val Ile Ala Leu Gly Cys Thr Cys Lys Leu Tyr Ala Ile Arg Thr Gln Glu Tyr Ser Ile Phe Ala Pro Leu Ser Arg Met Glu Ala Glu Ile Val Gln Gln Ala Pro Pro Ser Tyr Gly Gln Leu Ile Ala Gln Gly Ala Ile Pro Pro Val Glu Asp Phe Pro Thr Glu Asn Pro Asn Asp Asn Ser Val Leu Gly Asn Leu Arg Ser Leu Leu Gln Ile Leu 295 Arg Gln Asp Met Thr Pro Gly Gly Gly Pro Gly Ala Arg Arg Arg Gln 315 Arg Gly Arg Leu Met Arg Arg Leu Val Arg Arg Leu Arg Arg Trp Gly 325 330 Leu Leu Pro Arg Thr Asn Thr Pro Ala Arg Ala Ser Glu Ala Arg Ser 345 Gln Val Thr Pro Ser Ala Ala Pro Leu Glu Ala Leu Asp Gly Gly Thr Gly Pro Ala Arg Glu Gly Gly Ala Val Gly Gln Asp Gly Glu Gln Ala Pro Pro Leu Pro Ile Lys Ala Pro Leu Pro Ser Ala Ser Thr Ser 395 Pro Ala Pro Thr Thr Val Pro Glu Ala Pro Gly Pro Leu Pro Ser Leu 405 Pro Leu Glu Pro Ser Leu Leu Ser Gly Val Val Gln Ala Leu Arg Gly 425 Arg Leu Leu Pro Ser Leu Gly Pro Pro Gly Pro Thr Arg Ser Pro Pro

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Gly Pro His Thr Ala Val Leu Ala Leu Glu Asp Glu Asp Val Leu
    450
                        455
                                            460
Leu Val Pro Leu Ala Glu Pro Gly Val Trp Val Ala Glu Ala Glu Asp
                                        475
Glu Pro Leu Leu Thr
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                  5
His Gly Ala Gln Arg Asp Leu Lys Leu Gly Ser Arg Leu Tyr Gly Pro
                                 25
Ser Ser Val Xaa Phe Ala Glu Asp Phe Val Arg Ser Ser Lys Gln His
```

Tyr	Asn 50	Cys	Glu	His	Ser	Lys 55	Ile	Asn	Phe	Arg	Asp 60	Lys	Arg	Ser	Ala
Leu 65	Gln	Ser	Ile	Asn	Glu 70	Trp	Ala	Ala	Gln	Thr 75	Thr	Asp	Gly	Lys	Leu 80
Pro	Glu	Val	Thr	Lys 85	Asp	Val	Glu	Arg	Thr 90	Asp	Gly	Ala	Leu	Leu 95	Val
Asn	Ala	Met	Phe 100	Phe	Lys	Pro	His	Trp 105	Asp	Glu	Lys	Phe	His 110	His	Lys
Met	Val	Asp 115	Asn	Arg	Gly	Phe	Met 120	Val	Thr	Arg	Ser	Туг 125	Thr	Val	Gly
Val	Thr 130	Met	Met	His	Arg	Thr 135	Gly	Leu	Tyr	Asn	Tyr 140	Tyr	Asp	Asp	Glu
Lys 145	Glu	Lys	Leu	Gln	Met 150	Val	Glu	Met	Pro	Leu 155	Ala	His	Lys	Leu	Ser 160
Ser	Leu	Leu	Ile	Leu 165	Met	Pro	His	His	Val 170	Glu	Pro	Leu	Glu	Arg 175	Leu
Glu	Lys	Leu	Leu 180	Thr	Lys	Glu	Gln	Leu 185	Lys	Ile	Trp	Met	Gly 190	Lys	Met
Gln	Lys	Lys 195	Ala	Val	Ala	Ile	Ser 200	Leu	Pro	Lys	Gly	Val 205	Val	Glu	Val
Thr	His 210	Asp	Leu	Gln	Lys	His 215	Leu	Ala	Gly	Leu	Gly 220	Leu	Thr	Glu	Ala
Ile 225	Asp	Lys	Asn	Lys	Ala 230	Asp	Leu	Ser	Arg	Met 235	Ser	Gly	Lys	Lys	Asp 240
Leu	Tyr	Leu	Ala	Ser 245	Val	Phe	His	Ala	Thr 250	Ala	Phe	Glu	Trp	Asp 255	Thr
Glu	Gly	Asn	Pro 260	Phe	Asp	Gln	Asp	11e 265	Tyr	Gly	Arg	Glu	Glu 270	Leu	Arg
Ser	Pro	Lys 275	Xaa	Phe	Tyr	Ala	Asp 280	His	Pro	Phe	Ile	Phe 285	Leu	Val	Arg
Asp	Thr 290	Gln	Thr	Gly	Ser	Leu 295	Leu	Phe	Ile	Gly	Arg 300	Leu	Val	Arg	Pro
Lys 305	Gly	Asp	Lys	Met	Arg 310	Asp	Glu	Leu							

728

<210> 742 <211> 60 <212> PRT <213> Homo sapiens <400> 742 Arg Asn Ile Lys Trp Glu Lys Ala Tyr Lys Ala Phe Arg Ile Leu Ser Val Ser Ser Phe Leu Val Phe Arg Cys Tyr Val Ile Lys His Ile Phe 20 25 Phe Gly Phe Pro Arg Tyr Thr Ile Tyr Leu Phe Lys Gly Lys Ser Ile 40 Lys Cys Ile Tyr Phe Ile Leu Trp Phe Cys Tyr Leu 55 <210> 743 <211> 204 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (4) <223> Xaa equals any of the naturally occurring L-amino acids <400> 743 Pro Arg Gly Xaa Ser Gln Val Cys Pro Cys Ser Trp Asn Pro Gly Val Pro Glu Ala Lys Ala Pro Pro Arg Gly Ser Arg Glu Asp Leu Val Ala Glu Glu Ser Pro Glu Leu Leu Asn Pro Glu Pro Arg Arg Leu Ser Pro Glu Leu Arg Leu Leu Pro Tyr Met Ile Thr Leu Gly Asp Ala Val His 50 Asn Phe Ala Asp Gly Leu Ala Val Gly Ala Ala Phe Ala Ser Ser Trp Lys Thr Gly Leu Ala Thr Ser Leu Ala Val Phe Cys His Glu Leu Pro

729

His Glu Leu Gly Asp Phe Ala Ala Leu Leu His Ala Gly Leu Ser Val

Arg Gln Ala Leu Leu Leu Asn Leu Ala Ser Ala Leu Thr Ala Phe Ala 115 120 125

Gly Leu Tyr Val Ala Leu Ala Val Gly Val Ser Glu Glu Ser Glu Ala · 130 135 140

Trp Ile Leu Ala Val Ala Thr Gly Leu Phe Leu Tyr Val Ala Leu Cys 145 150 155 160

Asp Met Leu Pro Ala Met Leu Lys Val Arg Asp Pro Arg Pro Trp Leu 165 170 175

Leu Phe Leu Leu His Asn Val Gly Leu Leu Gly Gly Trp Thr Val Leu 180 185 190

Leu Leu Ser Leu Tyr Glu Asp Asp Ile Thr Phe 195 200

<210> 744

<211> 81

<212> PRT

<213> Homo sapiens

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<400> 744

Ile Thr Lys Gly Lys Xaa Val Ala Cys Ser Thr Gly Pro Glu Phe Pro 1 5 10 15

Gly Arg Pro Thr Arg Pro Thr Thr Glu Gly Tyr Gly Cys Glu Lys Thr
20 25 30

Thr Glu Gly Tyr Gly Cys Glu Lys Thr Thr Glu Gly Tyr Gly Cys Glu 35 40 45

Lys Thr Thr Glu Gly Tyr Gly Cys Glu Lys Thr Thr Glu Gly Tyr Gly 50 55 60

Cys Glu Lys Thr Thr Glu Gly Thr Ala Ala Arg Arg Arg Gln Arg Val 65 70 75 80

Arg

<21	1> 7	51													
<21	2> PI	T													
<21	3> H	omo s	sapie	ens											
<40	0> 74	15													
Leu	Pro	Pro	Leu	Gly	Ser	Pro	Gly	Pro	Ala	Arg	Ser	Ala	Gly	Ser	Cys
1				5			_		10					15	
Ser	Val	Leu	Phe	Ser	Leu	Ile	Leu	Gln	Ara	Gln	Asp	Pro	Ala	Pro	Ala
			20					25			•		30		
T.en	Ser	ጥከተ	Ala	Thr	Met	Glv	Lys	Glv	Val	Glv	Ara	Asp	Lvs	Tvr	Glu
Deu	-	35				011	40	U-1		,	5	45	-1-	-4-	
		33					••								
Pro	nla	A1 =	t/al	Sar	Glu	Gln	Gly	Δen	T.vc	T.ve	Glv	T.vc	Lvs	Glv	Lvs
FIU		AIG	VAI	261	GIU		GLy	nap	шуз	2,3	60	D , 0	2,0	1	-70
	50					55					00				
.	.			14 m.k.		61	T 0.11	T	t	C1	17-1	602	Mot	Acn	Aen
	Asp	Arg	ASP	met		GIU	Leu	гаг	гуя		vai	Ser	ne c	vah	80 V25
65					70					75					00
·	_	_		_	_		_		•	•		G1	mb		7
His	Lys	Leu	ser		Asp	Glu	Leu	HIS		гÀг	Tyr	GIY	Thr		rea.
				85					90					95	
		_				_						_	_ •	_	
Ser	Arg	Gly		Thr	Ser	Ala	Arg		Ala	Glu	Ile	Leu		Arg	Asp
			100					105					110		
													_		_
Gly	Pro	Asn	Ala	Leu	Thr	Pro	Pro	Pro	Thr	Thr	Pro		Trp	He	ràs
		115					120					125			
Phe		Arg	Gln	Leu	Phe		Gly	Phe	Ser	Met		Leu	Trp	Ile	GLY
	130					135					140				
									_		_				
Ala	Ile	Leu	Cys	Phe		Ala	Tyr	Ser	Ile		Ala	Ala	Thr	GLu	
145					150					155					160
											_			_	
Glu	Pro	Gln	Asn	Asp	Asn	Leu	Tyr	Leu	Gly	Val	Val	Leu	Ser		Val
				165					170					175	
Val	Ile	Ile	Thr	Gly	Cys	Phe	Ser	Tyr	Tyr	Gln	Glu	Ala	Lys	Ser	Ser
			180					185					190		
Lys	Ile	Met	Glu	Ser	Phe	Lys	Asn-	Met	Val	Pro	Gln	Gln	Ala	Leu	Val
		195					200					205			
Ile	Arg	Asn	Gly	Glu	Lys	Met	Ser	Ile	Asn	Ala	Glu	Glu	Val	Val	Val
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<210> 745

225	АЅР	Leu	vai	GIU	230	гур	GIY	GIY	АБР	235	116	PIO	NIG	nsp	240
Arg	Ile	Ile	Ser	Ala 245	Asn	Gly	Cys	Lys	Val 250	Asp	Asn	Ser	Ser	Leu 255	Thr
Gly	Glu	Ser	Glu 260	Pro	Gln	Thr	Arg	Ser 265	Pro	Asp	Phe	Thr	Asn 270	Glu	Asn
Pro	Leu	Glu 275	Thr	Arg	Asn	Ile	Ala 280	Phe	Phe	Ser	Thr	Asn 285	Cys	Val	Glu
Gly	Thr 290	Ala	Arg	Gly	Ile	Val 295	Val	Tyr	Thr	Gly	Asp 300	Arg	Thr	Val	Met
Gly 305	Arg	Ile	Ala	Thr	Leu 310	Ala	Ser	Gly	Leu	Glu 315	Gly	Gly	Gln	Thr	Pro 320
Ile	Ala	Ala	Glu	Ile 325	Glu	His	Phe	Ile	His 330	Ile	Ile	Thr	Gly	Val 335	Ala
Val	Phe	Leu	Gly 340	Val	Ser	Phe	Phe	11e 345	Leu	Ser	Leu	Ile	Leu 350	Glu	Tyr
Thr	Trp	Leu 355	Glu	Ala	Val	Ile	Phe 360	Leu	Ile	Gly	Ile	Ile 365	Val	Ala	Asn
Val	Pro 370	Glu	Gly	Leu	Leu	Ala 375	Thr	Val	Thr	Val	Cys 380	Leu	Thr	Leu	Thr
385	_				Arg 390	_				395					400
				405	Ser				410					415	
			420		Arg			425					430		
		435			Asp		440					445			
_	450				Thr	455					460				
465					Phe 470					475					480
Lys	Arg	Ala	Val	Ala 485	Gly	Asp	Ala	Ser	Glu 490	Ser	Ala	Leu	Leu	Lys 495	Суз

Ile	Glu	Leu	Cys 500	Cys	Gly	Ser	Val	Lys 505	Glu	Met	Arg	Glu	Arg 510	Tyr	Ala
Lys	Ile	Val 515	Glu	Ile	Pro	Phe	Asn 520	Ser	Thr	Asn	Lys	Tyr 525	Gln	Leu	Ser
Ile	His 530	Lys	Asn	Pro	Asn	Thr 535	Ser	Glu	Pro	Gln	His 540	Leu	Leu	Val	Met
Lys 545	Gly	Ala	Pro	Glu	Arg 550	Ile	Leu	Asp	Arg	Cys 555	Ser	Ser	Ile	Leu	Leu 560
His	Gly	Lys	Glu	Gln 565	Pro	Leu	Asp	Glu	Glu 570	Leu	Lys	Asp	Ala	Phe 575	Gln
Asn	Ala	Tyr	Leu 580	Glu	Leu	Gly	Gly	Leu 585	Gly	Glu	Arg	Val	Leu 590	Gly	Phe
Cys	His	Leu 595	Phe	Leu	Pro	Asp	Glu 600	Gln	Phe	Pro	Glu	Gly 605	Phe	Gln	Phe
Asp	Thr 610	Asp	Asp	Val	Asn	Phe 615	Pro	Ile	Asp	Asn	Leu 620	Cys	Phe	Val	Gly
Leu 625	Ile	Ser	Met	Ile	Asp 630	Pro	Pro	Arg	Ala	Ala 635	Val	Pro	Asp	Ala	Val 640
Gly	Lys	Cys	Arg	Ser 645	Ala	Gly	Ile	Lys	Val 650	Ile	Met	Val	Thr	Gly 655	Asp
His	Pro	Ile	Thr 660	Ala	Lys	Ala	Ile	Ala 665	Lys	Gly	Val	Gly	Ile 670	Ile	Ser
Glu	Gly	Asn 675	Glu	Thr	Val	Glu	Asp 680	Ile	Ala	Ala	Arg	Leu 685	Asn	Ile	Pro
Val	Ser 690	Gln	Val	Asn	Pro	Arg 695	Asp	Ala	Lys	Ala	Cys 700	Val	Val	His	Gly
Ser 705	Asp	Leu	Lys	Asp	Met 710	Thr	Ser	Glu	Gln	Leu 715	Asp	Asp	Ile	Leu	Lys 720
Tyr	His	Thr	Glu	Ile 725	Val	Phe	Ala	Lys	Thr 730	Ser	Pro	Gln	Gln	Lys 735	Leu
Ile	Ile	Val	Glu 740	Arg	Leu	Pro	Lys	Thr 745	Gly	Cys	Tyr	Arg	Gly 750	Leu	

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Ile Pro Ala Leu Trp Xaa Ala Xaa Val Gly Arg Ser Leu Glu Pro Arg
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Ser Leu Arg Ser Ala Trp Ala Thr Trp
            20
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Xaa Xaa Leu Gly Gly Arg Val Cys Ser Glu Pro Arg Trp Arg His Cys
Thr Pro Ala Trp Gly Thr Glu Arg Asp Ser Ile Ser Lys Lys Lys
                                 25
            20
Lys Lys Ile Lys Asn
        35
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<210> 748

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Asn Xaa Ala Leu Arg Asp Asp Val Ala Ala Gly Arg Arg Leu His
                                     10
Ile Lys Ala Val Cys Gln Ser Val Arg Glu Ala Thr Thr Ala Ser Gly
                                 25
Gly Met Asn Ala Ala Ser Pro Arg Leu Xaa Arg His Arg Xaa Asn Gly
                                                 45
         35
                             40
Xaa Tyr Phe Thr Leu Arg Glu Arg Leu Ile Thr Met Gln Lys Gln Leu
     50
                                             60
Gly Gly Asn Pro Glu Val Tyr
                     70
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Gly Phe Tyr Cys Gly Asp Asp Ser Ile Arg Tyr Pro Tyr Arg Pro Asp
                             40
         35
Thr Ile Thr His Gly Leu Met Ala Gly Val Thr Ile Thr Ala Thr Val
                         55
Ile Leu Val Ser Ala Gly Glu Ala Tyr Leu Val Tyr Thr Asp Arg Leu
                     70
                                        75
Tyr Ser Arg Ser Asp Phe Asn Asn Tyr Val Ala Ala Val Tyr Lys Val
                 85
                                     90
Leu Gly Thr Ser Cys Leu Gly Leu Pro
            100
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<212> PRT
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                                     10
Tyr Thr Leu Arg Lys Gln Met Asn Xaa Asn Leu Phe Ser Ser Phe Ile
                    25
Thr Pro Thr Ile Ile Gly Leu Pro Ile Val Ile Ile Xaa Thr Met Phe
                             40
Pro Ser Ile Asp Xaa Pro Ile Thr Tyr Pro Xaa Xaa Gln
                        55
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<211> 58
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Ser Asp Pro Glu Ala Glu Val Glu Glu Ser Ser Ser Gly Leu Arg Leu
Ser Leu Ile Lys Met Thr Thr Ser Gln Lys His Arg Asp Phe Val Ala
Xaa Pro Met Gly Glu Asn Gln Trp Gly Thr Trp Leu Gly Leu Val Xaa
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739

Ser Trp Ala Arg Asn Trp Lys Lys Gly Phe 50

35

<210> 753 <211> 73 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (48) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (51) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (52) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (53) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (63) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (71) <223> Xaa equals any of the naturally occurring L-amino acids <400> 753 Thr Leu His Ser Lys Gly Asn Lys Ser Trp Ser Ser Thr Ala Val Thr 10 Ala Ala Leu Glu Leu Val Gly Gly Pro Val Pro Asn Ser Pro Tyr Ser 20 25 Glu Ser Tyr Tyr Asn Ser Leu Ala Val Val Leu Gln Arg Arg Asp Xaa

40

Glu Asn Xaa Xaa Yaa Phe Arg Leu Val Cys Cys Val Glu Leu Xaa Ala

740

50 55 60 Asp Asn Asn Ser His Arg Xaa Gln Leu 65 70 <210> 754 <211> 116 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (17) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (43) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (62) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (67) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (68) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (81) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (84) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (87) <223> Xaa equals any of the naturally occurring L-amino acids

741

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Met Gly Ser Asp Tyr Ile Arg Glu Val Asn Val Val Lys Ser Ala Arg
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Xaa Gly Tyr Ser Lys Met Leu Leu Gly Val Tyr Ala Tyr Phe Ile Glu

30 20 25 His Lys Gln Arg Asn Thr Leu Ile Trp Leu Xaa Thr Asp Gly Asp Ala 40 Arg Glu Leu Tyr Glu Lys Pro Thr Leu Ser Pro Thr Ile Xaa Asp Ile 55 Pro Ser Xaa Xaa Gly Ala Gly Pro Val Val Trp Gln Lys Ser Thr Gly Xaa Asn Lys Xaa Asn His Xaa Xaa Val Ser Xaa Xaa Trp Gly Gly Pro Arg Asn Pro Ile Xaa Pro Ile Ser Xaa Trp Xaa Phe Xaa Asn Ser Xaa 100 105 Gly Pro Xaa Phe 115 <210> 755 <211> 148 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (4) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (120) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (135) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (137) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (138)

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<220> <221> SITE <222> (146) <223> Xaa equals any of the naturally occurring L-amino acids Ile Arg Gln Xaa Ile Asp Ile Arg Lys Asp Leu Tyr Ala Asn Asn Val 10 Leu Ser Gly Gly Thr Thr Met Tyr Pro Gly Ile Ala Asp Arg Met Gln Lys Glu Ile Thr Ala Leu Ala Pro Ser Thr Met Lys Ile Lys Ile Ile 45 40 Ala Pro Pro Glu Ala Gln Ile Leu Cys Leu Asp Arg Trp Leu His Pro 55 Gly Leu Ser Val His Leu Pro Ala Asp Val Asp Gln Gln Thr Gly Asn 70 75 Thr Val Lys Pro Gly Leu Pro Leu Ser Thr Ala Asn Ala Phe Leu Lys . 90 85 His Phe Ser Trp Phe Leu Phe Cys Leu Leu Gly Thr Gln Leu Trp Asn 100 105 Val Pro Val Gly Ile Tyr Gly Xaa Phe Ser Phe Phe Phe Gln Ile Ile 120 Pro Arg Ala Lys Val Leu Xaa Trp Xaa Xaa His Gly Val Phe Leu Asn 140 135 Lys Xaa Trp Lys 145 <210> 756 <211> 151 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (147) <223> Xaa equals any of the naturally occurring L-amino acids

Ala Glu Leu Ala Thr Thr Ser Thr Met Pro Tyr Gln Tyr Pro Ala Leu

<400> 756

15 10 1 Thr Pro Glu Gln Lys Lys Glu Leu Ser Asp Ile Ala His Arg Ile Val 25 Ala Pro Gly Lys Gly Ile Leu Ala Ala Asp Glu Ser Thr Gly Ser Ile Ala Lys Arg Leu Gln Ser Ile Gly Thr Glu Asn Thr Glu Glu Asn Arg 55 Arg Phe Tyr Arg Gln Leu Leu Thr Ala Asp Asp Arg Val Asn Pro 70 Cys Ile Gly Gly Val Ile Leu Phe His Glu Thr Leu Tyr Gln Lys Ala 90 Asp Asp Gly Arg Pro Phe Pro Gln Val Ile Lys Ser Lys Gly Gly Val Val Gly Ile Lys Val Asp Lys Gly Val Val Pro Leu Ala Gly Thr Asn 115 Gly Glu Thr Thr Gln Gly Leu Asp Gly Leu Ser Glu Arg Cys Ala 135 Gln Tyr Xaa Glu Gly Arg Ser <210> 757 <211> 94 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (21) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (44) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (48) <223> Xaa equals any of the naturally occurring L-amino acids

745

<220> <221> SITE <222> (91) <223> Xaa equals any of the naturally occurring L-amino acids <400> 757 Phe Val Thr Ile Leu Ser Ile Ile Ile Thr Leu Phe Phe Ile Phe Gln 10 Leu Lys Val Ser Xaa Tyr Ser Phe Pro Glu Asn Pro Glu Pro Lys Ser 20 Leu Thr Thr Ser Lys Ser Thr Thr Pro Trp Arg Xaa Gln Met Asn Xaa Asn Leu Phe Ser Ser Phe Ile Thr Pro Thr Ile Ile Gly Leu Pro Ile 55 Val Ile Ile Ile Thr Met Phe Pro Ser Ile Ile Phe Pro Ser Pro Thr 65 70 75 Arg Leu Ile Asn Asn Arg Leu Ile Ser Ile Xaa Thr Met Asp 85 90 <210> 758 <211> 115 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (2) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (5) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (11) <223> Xaa equals any of the naturally occurring L-amino acids <220>

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Arg Xaa Ala Leu Xaa Arg Leu Thr Ile Gly Xaa Ser Trp Tyr Ala Cys
                                     10
Arg Tyr Arg Ser Gly Ile Pro Gly Ser Thr His Ala Ser Xaa Arg Arg
                                 25
Gly Gln Leu Arg Ala Arg Gly Gly Gly Ala Xaa Pro Arg Gly Ala Met
         35
Xaa Asp Xaa Arg Ala Gly Ser Pro Arg Xaa Gly Pro Ala Ala Arg Asp
Val Ala Ala Met Ala Ser Pro Gln Leu Cys Arg Ala Leu Val Ser Ala
                     70
                                         75
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Gln Trp Val Ala Glu Ala Leu Arg Ala Pro Arg Ala Gly Ala Ala Ser
                 85
                                      90
Ala Ala Xaa Arg Thr Pro Pro Gly Xaa Leu Ala Gly Ser Trp Gly Ala
            100
                                 105
Arg Thr Xaa
        115
<210> 759
<211> 44
<212> PRT
<213> Homo sapiens
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<223> Xaa equals any of the naturally occurring L-amino acids

<220>

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<222> (43)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 759

Ile Ala Xaa Gly Arg Ser Arg Gly Ser Lys Leu Thr Trp Thr Cys Met
1 5 10 15

Xaa Arg His Ser Ser Ser Ile Val Ser Pro Lys Phe Asn Ser Leu Ala 20 25 30

Val Val Leu Gln Arg Arg Asp Trp Glu Xaa Xaa Lys 35 40

<210> 760

<211> 94

<212> PRT

PCT/US00/05881 WO 00/55173

748

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<213> Homo sapiens
<220>
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<221> SITE
<222> (91)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 760
Asn Asp Leu Val Glu Tyr Ser Pro Val Thr Glu Lys His Leu Thr Asp
                                     10
Gly Met Thr Val Arg Glu Leu Cys Ser Ala Ala Ile Thr Met Ser Asp
             20
                                 25
Asn Thr Ala Ala Asn Leu Leu Leu Thr Thr Ile Gly Gly Pro Lys Glu
                             40
Leu Thr Ala Phe Leu His Asn Met Gly Asp His Val Thr Arg Leu Asp
     50
                         55
                                             60
Arg Trp Glu Pro Glu Leu Asn Glu Ala Ile Pro Asn Asp Glu Arg Xaa
                     70
Thr Thr Met Pro Val Ala Met Ala Thr Thr Xaa Ala Asn Tyr
<210> 761
<211> 38
<212> PRT
<213> Homo sapiens
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<220> <221> SITE <222> (24)

749

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105

Ser Ser Pro Glu Phe Ser Lys Thr Leu Gln Leu Glu Tyr Arg Phe Glu 115 120 125

Thr Val Gln Lys Leu Arg Phe Gly Ile Tyr Asp Ile Asp Asn Lys Thr

Pro Glu Leu Arg Asp Asp Phe Leu Gly Gly Ala Glu Cys Ser Leu 145 150 155 160

Gly Gln Ile Val Ser Ser Gln Val Leu Thr Leu Pro Leu Met Leu Lys 165 170 175

Leu Glu Asn Leu Leu Gly Gly Gly Pro Ser Arg Ser Gln Leu Arg Asn 180 185 190

<210> 763

<211> 103

<212> PRT

<213> Homo sapiens

<220>

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<222> (96)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 763

Ser Phe Tyr Ser Ile Pro Glu Phe Asp Glu Trp Lys Lys His Ile Glu
1 5 10 15

Asn Gln Lys Ala Trp Lys Ile Lys Tyr Tyr Lys Gly Leu Gly Thr Ser 20 25 30

Thr Ala Lys Glu Ala Lys Glu Tyr Phe Ala Asp Met Glu Arg His Arg
35 40 45

Ile Leu Phe Arg Tyr Ala Gly Pro Glu Asp Asp Ala Ala Ile Thr Leu 50 55 60

Ala Phe Ser Lys Lys Lys Ile Asp Asp Arg Lys Glu Trp Leu Thr Asn 65 70 75 80

Phe Met Glu Asp Arg Arg Gln Arg Ser Tyr Met Ala Tyr Gln Arg Xaa 85 90 95

Asp Ser Leu Ser Thr Gln Thr

PCT/US00/05881 WO 00/55173

751

<210> 764 <211> 105 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (101) <223> Xaa equals any of the naturally occurring L-amino acids Val Phe Ser Pro Thr Gly Ser Asp Gly Pro Leu Ala Thr Ser Lys Pro Val Pro Ala Glu Lys Ser Gly Leu Pro Val Gly Pro Glu Asn Gly Val 25 Glu Leu Ser Lys Glu Glu Leu Ile Arg Arg Lys Arg Glu Glu Phe Ile Gln Lys His Gly Arg Gly Met Glu Lys Ser Asn Lys Ser Thr Lys Ser Asp Ala Pro Lys Glu Lys Gly Lys Lys Ala Pro Arg Val Trp Glu Leu 70 75 Gly Gly Cys Ala Asn Lys Glu Met Leu Asp Tyr Ser Thr Ser Thr Thr 90 Asn Gly Thr Pro Xaa Ala Cys Leu Val 100 <210> 765 <211> 147 <212> PRT

<400> 765

<213> Homo sapiens

Gly Arg Glu Thr Met Phe Arg Ala Ala Ala Pro Gly Gln Leu Arg Arg

Ala Ala Ser Leu Leu Arg Phe Gln Ser Thr Leu Val Ile Ala Glu His 20

Ala Asn Asp Ser Leu Ala Pro Ile Thr Leu Asn Thr Ile Thr Ala Ala 35 40 45

752

Thr Arg Leu Gly Gly Glu Val Ser Cys Leu Val Ala Gly Thr Lys Cys
50 55 60

Asp Lys Val Ala Gln Asp Leu Cys Lys Val Ala Gly Ile Ala Lys Val 65 70 75 80

Leu Val Ala Gln His Asp Val Tyr Lys Gly Leu Leu Pro Glu Glu Leu 85 90 95

Thr Pro Leu Ile Leu Ala Thr Gln Lys Gln Phe Asn Tyr Thr His Ile 100 105 110

Cys Ala Gly Ala Ser Ala Phe Gly Lys Asn Leu Leu Pro Arg Val Ala 115 120 125

Ala Lys Leu Glu Val Ala Pro Ile Ser Asp Ile Ile Ala Ile Lys Ser 130 135 140

Pro Asp Thr 145

<210> 766

<211> 36

<212> PRT

<213> Homo sapiens

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<222> (7)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (18)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 766

Gly Arg Glu Ala Glu Ala Xaa Gln Leu Glu Ser Ser Lys Arg Phe Ala 1 5 10 15

Lys Xaa Phe Met Asp Arg His Gly Ile Pro Thr Ala Gln Trp Glu Gly
20 25 30

Phe His Gln Thr

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<210> 767
<211> 105
<212> PRT
<213> Homo sapiens
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Arg Phe Ala Leu Ser Thr Lys Ile Pro Asp Thr Lys Gly Cys Leu Gln
                                     10
Cys Arg Val Val Arg Asn Pro Tyr Thr Gly Ala Thr Phe Leu Leu Ala
                                 25
Ala Leu Pro Thr Ser Leu Leu Leu Gln Trp Tyr Glu Pro Leu Gln
         35
                             40
                                                 45
Lys Phe Leu Leu Lys Asn Phe Ser Ser Pro Leu Pro Xaa Pro Ala
Gly Met Leu Xaa Pro Leu Val Leu Asp Gly Lys Glu Leu Pro Gln Xaa
                     70
                                         75
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Phe Phe Gly Ala Glu Gly Pro Lys Gly Pro Gly Cys Arg Phe Leu Phe 85 90 95

Gln Xaa Leu Xaa Leu Gly Gly Trp Xaa 100 105

<210> 768

<211> 154

<212> PRT

<213> Homo sapiens

<400> 768

Val Thr Leu Thr Gln Cys Ser Glu Lys Leu Val Gln Leu Ile Leu His 1 5 10 15

Glu Tyr Lys Ile Phe Asn Ala Glu Val Leu Phe Arg Glu Asp Cys Ser 20 25 30

Pro Asp Glu Phe Ile Asp Val Ile Val Gly Asn Arg Val Tyr Met Pro 35 40 45

Cys Leu Tyr Val Tyr Asn Lys Ile Asp Gln Ile Ser Met Glu Glu Val

Asp Arg Leu Ala Arg Lys Pro Asn Ser Val Val Ile Ser Cys Gly Met 65 70 75 80

Lys Leu Asn Leu Asp Tyr Leu Leu Glu Met Leu Trp Glu Tyr Leu Ala 85 90 95

Leu Thr Cys Ile Tyr Thr Lys Lys Arg Gly Gln Arg Pro Asp Phe Thr
100 105 110

Asp Ala Ile Ile Leu Arg Lys Gly Ala Ser Val Glu His Val Gly Thr 115 120 125

Ser Thr Lys Tyr Ser Pro Gln Arg Val Gly Leu Thr His Thr Met Glu 130 135 140

His Glu Asp Val Ile Gln Ile Val Lys Lys 145 150

<210> 769

<211> 89

<212> PRT

<213> Homo sapiens

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Asn Gln Ala Gly Leu Thr Ala Asp Arg Met Leu Val Leu Ser Arg Ala
                                      10
Gly Gln Ala Ala Gly Leu Thr Phe Asn Gln Thr Ser Glu Ser Leu Ser
Ala Leu Val Lys Ala Gly Val Ser Gly Glu Ala Gln Ile Ala Ser Ile
Ser Gln Ser Val Ala Arg Phe Xaa Ser Ala Ser Gly Val Glu Val Asp
     50
Lys Val Val Glu Ala Phe Glu Gly Gly Pro Tyr Pro Phe Ala Tyr Ser
Lys Arg Ile Xaa Ile Ile Ala Val Phe
<210> 770
<211> 85
<212> PRT
<213> Homo sapiens
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<223> Xaa equals any of the naturally occurring L-amino acids

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20 25 30

Leu Ser Gln Leu Leu Pro Tyr Met Glu Asn Lys Lys Gly Ala Val Xaa 35 40 45

Leu Xaa Ser Ser Ile Ala Ala Tyr Asn Pro Val Val Ala Leu Gly Val 50 55 60

Tyr Asn Val Ser Lys Xaa Glu Leu Leu Gly Ser His 65 70 75

<210> 772

<211> 105

<212> PRT

<213> Homo sapiens

<220>

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<400> 772

Gly Ala Glu Glu Gly Arg Gln Glu Ala Gln Gly Xaa Arg Lys Glu Ser 1 5 10 15

Tyr Ser Val Tyr Val Tyr Lys Val Leu Lys Gln Val His Pro Asp Thr 20 25 30

Gly Ile Ser Ser Lys Ala Met Gly Ile Met Asn Ser Phe Val Asn Asp 35 40 45

Ile Phe Glu Arg Ile Ala Gly Glu Ala Ser Arg Leu Ala His Tyr Asn 50 55 60

Lys Arg Ser Thr Ile Thr Ser Arg Glu Ile Gln Thr Ala Val Arg Leu 65 70 75 80

Leu Leu Pro Gly Glu Leu Ala Lys His Ala Val Ser Glu Gly Thr Lys 85 90 95

Ala Val Thr Lys Tyr Thr Ser Ala Lys 100 105

<210> 773

<211> 144

<212> PRT

<213> Homo sapiens

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<220>
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<222> (139)
<223> Xaa equals any of the naturally occurring L-amino acids
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<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (141)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 773
Phe Ala His Leu Pro Lys Ser Thr Phe Val Leu Asp Glu Phe Lys Arg
                                    10
                 5
Lys Tyr Ser Asn Glu Asp Thr Leu Ser Val Ala Leu Pro Tyr Phe Trp
Glu His Phe Asp Lys Asp Gly Trp Ser Leu Trp Tyr Ser Glu Tyr Arg
                             40
Phe Pro Glu Glu Leu Thr Gln Thr Phe Met Ser Cys Asn Leu Ile Thr
                         55
Gly Met Phe Gln Arg Leu Asp Lys Leu Arg Lys Asn Ala Phe Ala Ser
                    70
Val Ile Leu Phe Gly Thr Asn Asn Ser Ser Ser Ile Ser Gly Val Trp
                 85
Val Xaa Pro Gly Gln Glu Leu Ala Phe Pro Leu Ser Pro Asp Trp Gln
            100
Val Asp Tyr Glu Val Ile His Met Ala Glu Thr Gly Ser Gly Lys Arg
                            120
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Gly Asp Pro Xaa Ala Gly Ser Arg Val Leu Xaa Xaa Xaa Arg Gly Pro 135 140 130

<210> 774

<211> 64

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (7)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (56)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 774

Ile Arg His Glu Arg Glu Xaa Glu Gln Gly Val Tyr Thr Cys Thr Ala 5 10 1

Gln Gly Ile Trp Lys Asn Glu Gln Lys Gly Glu Lys Ile Pro Arg Cys 20 25

Leu Pro Val Cys Gly Lys Pro Val Asn Pro Val Glu Gln Arg Gln Arg 40

Ile Ile Gly Gly Gln Lys Ala Xaa Gly Ile Val Gly Ala Phe Leu Gln 50 55

<210> 775

<211> 69

<212> PRT

<213> Homo sapiens

<400> 775

Asn Ile Ser Asn Ser Gln Val Asn Arg Leu Arg His Phe Val Arg Ala

Gly Leu Arg Ser Leu Phe Arg Pro Glu Pro Gln Thr Ala Val Glu Trp

. 30 20 25 Ala Asp Ala Asn Tyr Tyr Leu Pro Lys Glu Ser Ala Tyr Gln Glu Gly 40 45 Arg Trp Glu Thr Leu Pro Phe Gln Arg Ala Ile Met Asn Ala Asn Gly 50 55 Gln Arg Leu His Pro 65 <210> 776 <211> 56 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (5) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (15) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (31) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (54) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (55) <223> Xaa equals any of the naturally occurring L-amino acids <400> 776 Glu Arg Val Phe Xaa Pro His Gly Leu Ile Met Asp Arg Thr Xaa Arg Phe Ala Arg Asn Val Met Lys Glu Met Gly Gly His His Ile Xaa Val 20 25

Leu Phe Leu Leu Lys Gly Gly Tyr Lys Phe Phe Ala Asp Leu Leu Asp

40 45 35 Tyr Ile Lys Gly Leu Xaa Xaa Lys 50 <210> 777 <211> 134 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (4) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (5) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (6) <223> Xaa equals any of the naturally occurring L-amino acids <400> 777 Leu Gln Phe Xaa Xaa Xaa Met Ile Thr Pro Ser Ser Asn Thr Thr His Tyr Arg Glu Ser Trp Tyr Ala Cys Arg Tyr Arg Ser Gly Ile Pro Gly 20 Ser Thr His Ala Ser Gly Val Phe Glu Val His Lys Lys Asn Val Arg Gly Glu Phe Thr Tyr Glu Ile Gln Asp Asn Thr Gly Lys Met Glu 55 Val Val His Gly Arg Leu Thr Thr Ile Asn Cys Glu Glu Gly Asp 65 Lys Leu Lys Leu Thr Cys Phe Glu Leu Ala Pro Lys Ser Gly Asn Thr Gly Glu Leu Arg Ser Val Ile His Ser His Ile Lys Val Ile Lys Thr 100

Arg Lys Asn Lys Lys Asp Ile Leu Asn Pro Asp Ser Ser Met Glu Thr

125

120

PCT/US00/05881 WO 00/55173

762

Ser Pro Asp Phe Phe Phe 130

<210> 778

<211> 133

<212> PRT

<213> Homo sapiens

<400> 778

Thr Ile Thr Ser Gly Gly Asn Pro Pro Ala Phe Ser Leu Thr Pro Asp

Gly Lys Leu Thr Ala Lys Asn Ala Asp Ile Ser Gly Ser Val Asn Ala 25

Asn Ser Gly Thr Leu Ser Asn Val Thr Ile Ala Glu Asn Cys Thr Ile 35 40

Asn Gly Thr Leu Arg Ala Glu Lys Ile Val Gly Asp Ile Val Lys Ala 55

Ala Ser Ala Ala Phe Pro Arg Gln Val Glu Ser Ser Val Asp Trp Pro 70 75

Ser Gly Thr Arg Thr Val Thr Val Thr Asp Asp His Pro Phe Asp Arg 90

Gln Ile Val Val Leu Pro Leu Thr Phe Arg Gly Ser Lys Arg Thr Val 105

Ser Gly Arg Thr Thr Tyr Ser Met Cys Tyr Leu Lys Val Leu Met Asn 115 120

Gly Ala Val Ile Tyr 130

<210> 779

<211> 90

<212> PRT

<213> Homo sapiens

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Pro Asn Thr Ala Leu Val Gly Val Gln Val Asp Ser Glu Gln Phe Gly
Ser Gln Gln Val Ser Arg Asn Tyr His Leu Arg Gly Arg Ile Leu Gln
                                 25
             20
Val Pro Ser Asn Tyr Asn Pro Gln Thr Arg Gln Tyr Ser Gly Ile Trp
                             40
Asp Gly Thr Xaa Lys Pro Ala Tyr Ser Asn Asn Met Ala Trp Xaa Leu
                         55
Trp Asp Met Leu Thr His Pro Arg Tyr Gly Met Gly Lys Arg Leu Gly
                                        75
                     70
65
Ala Ala Asp Val Asp Lys Trp Ala Leu Tyr
                 85
<210> 780
<211> 82
<212> PRT
<213> Homo sapiens
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<400> 780
Val Xaa Arg Ala Ser Asp Asp Ala Glu Gly Tyr Leu Asp Xaa Phe Lys
                  5
                                     10
Gly Lys Ile Thr Glu Ser His Leu Xaa Lys Glu Leu Leu Glu Lys Val
                                 25
             20
Glu Leu Thr Glu Asp Asn Ala Ser Arg Leu Glu Glu Phe Ser Lys Xaa
                             40
Trp Lys Asp Ala Ser Xaa Lys Trp Asn Ala Met Trp Ala Xaa Lys Ile
                                              60
     50
                         55
Xaa Gln Thr Lys Asp Xaa Lys Arg Xaa Leu Phe Cys Tyr Leu Val Val
 65
                     70
                                          75
Arg Ser
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<210> 781

<211> 49

<212> PRT

<213> Homo sapiens

PCT/US00/05881 WO 00/55173

765

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Tyr Leu Asp Asn Leu Glu Ala Thr Gly Leu Tyr Gln Val Pro Leu Ser
                                 25
Ala Ala Gln Pro Gly Asp Val Leu Leu Cys Xaa Phe Gly Ser Ser Xaa
                             40
                                                 45
Xaa
<210> 782
<211> 85
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Xaa Lys Glu Asn Gly Thr Val Thr Ala Ala Asn Ala Ser Thr Leu Asn
Asp Gly Ala Ala Ala Leu Val Leu Met Thr Ala Asp Ala Ala Xaa Arg
             20
                                 25
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Leu Asn Val Thr Pro Leu Ala Arg Ile Val Ala Phe Ala Asp Ala Ala
Val Glu Pro Ile Asp Phe Pro Ile Ala Pro Val Tyr Ala Ala Ser Met
                  55
Val Leu Lys Asp Val Gly Leu Lys Lys Glu Asp Ile Ala Met Trp Glu
                    70
                                        75
Val Asn Gly Ser Leu
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767

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Gly Pro Glu Phe Pro Gly Arg Pro Thr Arg Pro Leu Leu Cys Leu Glu
                                 25
Gly Ile Ile Leu Ser Leu Phe Val Ile Ile Thr Ile Thr Ile Leu Ile
                             40
Asn His Leu Thr Leu Ala Ser Ile Thr Pro Ile Ile Leu Leu Val Xaa
                         55
     50
Ala Ala Cys Glu Ala Xaa Leu Gly Leu Ile Pro Phe Ser Tyr Xaa Leu
                                         75
                     70
Xaa Tyr Ile Arg
<210> 785
<211> 61
<212> PRT
<213> Homo sapiens
<400> 785
Ile Gly Phe Asp Asn Lys Lys Asp Leu Leu Ile Ser Val Gly Asp Leu
Val Asp Arg Gly Ala Glu Asn Val Glu Cys Leu Glu Leu Ile Thr Phe
```

25

769

```
Pro Trp Phe Arg Ala Val Arg Gly Asn His Glu Gln Met Met Ile Asp
                              40
Gly Leu Ser Glu Arg Gly Asn Val Asn His Trp Leu Leu
                        55
<210> 786
<211> 102
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Gly Leu Gln Pro Tyr Cys Tyr Xaa Thr Trp Arg Cys Arg Cys Thr Thr
Gly Gln Pro Gly Thr Ala Pro Ala Gly Thr Pro Gly Ala Pro Pro Leu
```

25

Xaa Gly Met Ala Ile Val Lys Glu Glu Glu Thr Glu Ala Ala Ile Gly

40

35

Ala Pro Pro Thr Ala Thr Glu Gly Pro Glu Thr Lys Pro Val Leu Xaa 55 Ala Leu Glu Glu Gly Pro Gly Ala Glu Gly Ser Arg Leu Asp Ser Leu 70 Val Ala Xaa Xaa Leu Xaa Leu Glu Val Val Ala Leu Arg Asp Ser Ala 90 85 Pro Val Leu Ala Gly Thr 100 <210> 787 <211> 64 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (3) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (7) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (44) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (48) <223> Xaa equals any of the naturally occurring L-amino acids <400> 787 Cys Leu Xaa Arg Ala Arg Xaa Pro Ala Ala Ala Asn Ser Ser Gly Asp Gly Gly Ala Ala Gly Asp Gly Thr Val Val Asp Cys Pro Val Cys Lys 20 Gln Gln Cys Phe Ser Lys Asp Ile Val Glu Asn Xaa Phe Met Arg Xaa 40 45 35

Ser Gly Ser Lys Ala Ala Thr Asp Ala Gln Asp Ala Asn Gln Cys Cys 50 55

<210> 788

<211> 61

<212> PRT

<213> Homo sapiens

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Thr Leu Ala Phe Phe Leu Ile Pro Cys Ile Gly Ser Pro Ala Cys Pro 5 10

Thr Met Ser Asp Ala Ala Val Asp Thr Ser Ser Glu Ile Thr Thr Lys

Asp Leu Lys Glu Lys Lys Glu Val Leu Glu Arg Gly Arg Lys Trp Lys

Arg Arg Pro Xaa Leu Thr Gly Asn Ala Asn Leu Gly Lys 55

<210> 789

<211> 69

<212> PRT

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<400> 789

Ala Gln Asp Asn Phe Lys His Leu Asn Gly Ile Xaa Leu Phe His Cys 10

Ile Asp Pro Asn Gly Ser Lys His Lys Arg Thr Asp Arg Ser Ile Leu 20 25

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Cys Cys Leu Arg Lys Gly Glu Ser Gly Gln Ser Trp Gln Gly Leu Thr
         35
Lys Glu Arg Ala Lys Leu Asn Trp Leu Ser Val Asp Phe Asn Asn Trp
                         55
Glu Arg Leu Gly Arg
 65
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Gln Ser Thr Val Lys Leu Glu His Ala Lys Ser Val Ala Ser Arg Ala
                  5
                                     10
                                                          15
Thr Val Leu Gln Lys Xaa Ser Xaa Thr Pro Val Gly Met Phe Leu Lys
             20
                                 25
Leu Asn Xaa Met Asn Val Lys Phe Xaa Ser Gly Tyr Tyr Glu Leu Pro
                             40
                                                 45
Cys Arg Ser
    50
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PCT/US00/05881 WO 00/55173

773

<210> 791

<211> 154

<212> PRT

<213> Homo sapiens

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<222> (78)

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<400> 791

Asp Pro Gln Ala His Val Ala Met Leu Ser Ser Thr Ala Met Tyr Ser

Ala Pro Gly Arg Asp Leu Gly Met Glu Pro His Arg Ala Ala Gly Pro 25

Leu Gln Leu Arg Phe Ser Pro Tyr Val Phe Asn Gly Gly Thr Ile Leu

Ala Ile Ala Gly Glu Asp Phe Ala Ile Val Ala Ser Asp Thr Arg Leu 55

Ser Glu Gly Phe Ser Ile His Thr Arg Asp Ser Pro Lys Xaa Tyr Lys

Leu Thr Asp Lys Thr Val Ile Gly Cys Ser Gly Phe His Gly Asp Cys 90

Leu Thr Leu Thr Lys Ile Ile Glu Ala Arg Leu Lys Met Tyr Lys His

Ser Asn Asn Lys Ala Met Thr Thr Gly Ala Ile Ala Ala Met Leu Ser

Thr Ile Leu Tyr Ser Arg Arg Phe Phe Pro Tyr Tyr Val Tyr Asn Ile 135 140

Ile Gly Gly Leu Asp Glu Glu Gly Lys Gly 145

<210> 792

<211> 96

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<210> 793

<211> 72

<212> PRT

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<400> 793

Arg Pro Pro Val Arg Xaa Phe Leu Arg Asp Phe Phe Met Ser Met Tyr
1 5 10 15

Thr Thr Ala Gln Leu Leu Ala Ala Asn Glu Gln Lys Phe Lys Phe Asp

775

20 25 30

Pro Leu Phe Leu Arg Leu Phe Phe Arg Glu Ser Tyr Pro Phe Thr Thr 35 40 45

Glu Glu Ser Leu Ser Leu Thr Asn Ser Gly Thr Gly Lys His Gly Ala
50 60

Val Arg Phe Ala Asp Cys Phe Arg 65 70

<210> 794

<211> 124

<212> PRT

<213> Homo sapiens

<400> 794

Gly Ser Gly Asp His Glu Gly Gly Lys Gly Asp Gly Met Glu Glu Val 1 5 10 15

Pro His Asp Cys Pro Gly Ala Asp Ser Ala Gln Ala Gly Arg Gly Ala 20 25 30

Ser Cys Gln Gly Cys Pro Asn Gln Arg Leu Cys Ala Ser Gly Ala Gly 35 40 45

Ala Thr Pro Asp Thr Ala Ile Glu Glu Ile Lys Glu Lys Met Lys Thr 50 60

Val Lys His Lys Ile Leu Val Leu Ser Gly Lys Gly Gly Val Gly Lys 65 70 75 80

Ser Thr Phe Ser Ala His Leu Ala His Gly Leu Ala Glu Asp Glu Asn 85 90 95

Thr Gln Ile Ala Leu Leu Asp Ile Asp Ile Cys Gly Pro Ser Ile Pro 100 105 110

Lys Ile Met Gly Leu Glu Gly Glu Gln Val His Gln
115 120

<210> 795

<211> 144

<212> PRT

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  Thr Lys Xaa Arg Thr Glu Xaa Val Gln Lys Leu Cys Pro Gly Gln
                                   25
  Xaa Pro Phe Leu Leu Tyr Xaa Thr Glu Val His Thr Asp Thr Asn Lys
                                                    45
           35
                               40
  Xaa Ala Glu Phe Leu Xaa Ala Val Leu Cys Pro Pro Arg Tyr Pro Xaa
       50
                           55
```

Leu Ala Ala Leu Asn Pro Xaa Ser Asn Thr Ala Xaa Leu Xaa Ile Phe

779

 Asn
 Leu
 Club
 Club
 Leu
 <td

Lys Val Ser Leu Arg Arg Ser Xaa Trp Ile Ala Arg Ala His Pro Gly

135

<210> 796 <211> 97 <212> PRT

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<400> 796

Ile Met Lys Asn Gly Phe Tyr Ala Thr Tyr Arg Ser Lys Asn Lys Gly
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Lys Asp Lys Arg Ser Ile Asn Leu Ser Val Phe Leu Asn Ser Xaa Leu 20 25 30

Ala Asp Asn His His Leu Gln Val Gly Ser Asn Tyr Leu Tyr Ile His

Lys Ile Asp Gly Lys Thr Phe Leu Phe Thr Lys Thr Asn Asp Lys Ser 50 55 60

Leu Val Gln Lys Ile Asn Arg Ser Lys Ala Ser Val Glu Asp Ile Lys 65 70 75 80

Asn Ser Leu Val Asp Asp Gly Ile Ile Gly Ile Pro Ile Phe Phe Val 85 90 95

Cys

<210> 797 <211> 181 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (2) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (3) <223> Xaa equals any of the naturally occurring L-amino acids Arg Xaa Xaa Pro Ser Leu Lys Gly Thr Lys Ala Gly Ala Pro Pro Arg 10 Cys Gly Arg Ser Arg Thr Ser Gly Ser Pro Gly Leu Gln Glu Phe Gly 25 Thr Arg Pro Ser Arg Leu Arg Lys Thr Arg Lys Leu Arg Gly His Val 40 45 Ser His Gly His Gly Arg Ile Gly Lys His Arg Lys His Pro Gly Gly Arg Gly Asn Ala Gly Gly Leu His His His Arg Ile Asn Phe Asp Lys 70 75 Tyr His Pro Gly Tyr Phe Gly Lys Val Gly Met Lys His Tyr His Leu 90 Lys Arg Asn Gln Ser Phe Cys Pro Thr Val Asn Leu Asp Lys Leu Trp 105 Thr Leu Val Ser Glu Gln Thr Arg Val Asn Ala Ala Lys Asn Lys Thr 120 Gly Ala Ala Pro Ile Ile Asp Val Val Arg Ser Gly Tyr Tyr Lys Val 130 135 Leu Gly Lys Gly Lys Leu Pro Lys Gln Pro Val Ile Val Lys Ala Lys 155 Phe Phe Ser Arg Arg Ala Glu Glu Lys Ile Lys Ser Val Gly Gly Ala 165 170

781

Cys Val Leu Val Ala 180

<210> 798

<211> 136

<212> PRT

<213> Homo sapiens

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<400> 798

Trp Ile Pro Arg Ala Ala Gly Ile Arg His Glu Arg Lys Glu Gly Trp

1 5 10 15

Arg Glu Glu Lys Gly Pro Phe Cys His Gln Arg Arg Xaa Thr Arg Glu 20 25 30

Tyr Thr Ile Asn Ile His Lys Arg Ile His Gly Val Gly Phe Lys Lys
35 40 45

Arg Ala Pro Arg Ala Leu Lys Glu Ile Arg Lys Phe Ala Met Lys Glu 50 55 60

Met Gly Thr Pro Asp Val Arg Ile Asp Thr Arg Leu Asn Lys Ala Val 65 70 75 80

Trp Ala Lys Gly Ile Arg Asn Val Pro Tyr Arg Ile Arg Val Arg Leu 85 90 95

Ser Arg Lys Arg Asn Glu Asp Glu Asp Ser Pro Asn Lys Leu Tyr Thr 100 105 110

Leu Val Thr Tyr Val Pro Val Thr Thr Phe Lys Ile Ser Val Leu Asn 115 120 125

Ser Val Thr Val Ala Lys Ser Pro 130 135

<210> 799

<211> 142

<212> PRT

<213> Homo sapiens

<400> 799

Trp Ile Pro Arg Ala Ala Gly Ile Arg His Glu Ala Ala Leu Ala Ala 10 Cys Ala Ala Met Ala Lys Ile Lys Ala Arg Asp Leu Arg Gly Lys Lys Lys Glu Glu Leu Leu Lys Gln Leu Asp Asp Leu Lys Val Glu Leu Ser Gln Leu Arg Val Ala Lys Val Thr Gly Gly Ala Ala Ser Lys Leu Ser 55 Lys Ile Arg Val Val Arg Lys Ser Ile Ala Arg Val Leu Thr Val Ile Asn Gln Thr Gln Lys Glu Asn Leu Arg Lys Phe Tyr Lys Gly Lys Lys 85 90 Tyr Lys Pro Leu Asp Leu Arg Pro Lys Lys Thr Arg Ala Met Arg Arg 100 105 Arg Leu Asn Lys His Glu Glu Asn Leu Lys Thr Lys Lys Gln Gln Arg 120 Lys Glu Arg Leu Tyr Pro Leu Arg Lys Tyr Ala Val Lys Ala 130 135 <210> 800 <211> 74 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (1) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (14)

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<400> 800
Xaa Xaa Tyr His Lys Tyr Lys Ala Lys Arg Asn Cys Trp Xaa Xaa Val
                                     10
Arg Gly Val Xaa Met Asn Pro Val Glu His Pro Phe Gly Gly Asn
                                                     30
             20
His Gln His Ile Gly Lys Pro Ser Thr Ile Arg Arg Asp Ala Pro Ala
                             40
Gly Arg Lys Val Gly Leu Ile Ala Ala Xaa Xaa Xaa Gly Xaa Leu Xaa
     50
                         55
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Gly Thr Lys Xaa Val Gln Glu Lys Glu Asn 65

<210> 801

<211> 100

<212> PRT

<213> Homo sapiens

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Met Thr Pro Val Gln Arg Gly Gly Pro Gly Ala Xaa Val Ala Leu Gly 10

Trp Gly Thr Ala Val Ala Ser Ala Arg Phe Arg Gln Trp His Pro Gly 20 25

Pro Gly Ser Arg Pro Trp Thr Gly Pro Gly Pro Arg Pro Arg Thr Arg 40

Xaa Gly Lys Ala Glu Asp Lys Glu Trp Met Pro Val Thr Lys Leu Gly 55

Arg Leu Val Lys Asp Met Lys Ile Lys Ser Leu Glu Glu Ile Tyr Leu 70 65

Phe Ser Leu Pro Ile Lys Glu Ser Glu Ile Ile Asp Ser Ser Trp Gly 90 85

Leu Ser Gln Gly 100

<210> 802

<211> 19

<212> PRT

<213> Homo sapiens

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<223> Xaa equals any of the naturally occurring L-amino acids
<400> 802
Xaa Glu Thr Gln Ala Ile Val Cys Gln Gln Leu Asp Leu Thr His Leu
Lys Gly Ala
<210> 803
<211> 54
<212> PRT
<213> Homo sapiens
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<400> 803
Gly Thr Arg Asp Val Arg Arg Val Pro Gly Val Ala Pro Thr Leu Val
                                     10
Arg Ser Ala Ser Glu Thr Ser Glu Lys Arg Pro Phe Met Cys Ala Tyr
                                 25
Pro Gly Cys Asn Lys Arg Tyr Phe Lys Leu Ser His Leu Gln Met His
         35
                             40
Ser Arg Xaa Ala His Trp
     50
<210> 804
<211> 140
<212> PRT
<213> Homo sapiens
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<222> (98)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (104)
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<223> Xaa equals any of the naturally occurring L-amino acids

786

<220> <221> SITE <222> (120) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (135) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (136) <223> Xaa equals any of the naturally occurring L-amino acids <400> 804 Phe Lys Ser Tyr Leu Gly Asp Thr Ile Glu Gly Ser Leu Gln Val Thr Gly Pro Glu Ile Pro Gly Ser Thr His Ala Ser Ala Glu Ser Leu Ser 20 Arg Arg Lys Leu Asp Thr Gly Thr Gly Ser Ala Met Arg Leu Leu Pro Arg Leu Leu Leu Leu Leu Leu Val Phe Pro Ala Thr Val Leu Phe 55 Arg Gly Gly Pro Arg Gly Leu Leu Ala Val Ala Gln Asp Leu Thr Glu 70 75 65 Asp Glu Glu Thr Val Glu Asp Ser Ile Ile Glu Asp Glu Asp Asp Glu Ala Xaa Val Glu Glu Asp Glu Xaa Thr Asp Phe Val Glu Asp Lys Glu 100 Glu Glu Asp Val Ser Gly Glu Xaa Glu Thr Leu Pro Ser Ala Asp Thr 115 120 Thr Ile Leu Phe Leu Lys Xaa Xaa Ile Phe Arg Gln

135

<210> 805

<211> 130

<212> PRT

<213> Homo sapiens

787

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<400> 805
Phe Glu Ala Asn Arg Gln Arg Ala Thr Met Ala Val Ala Arg Ala Ala
                  5
Leu Gly Pro Leu Val Thr Gly Leu Tyr Asp Val Gln Ala Phe Lys Phe
Gly Asp Phe Val Leu Lys Ser Gly Leu Ser Ser Pro Ile Tyr Ile Asp
                            40
Leu Arg Gly Ile Val Ser Arg Pro Arg Leu Leu Ser Gln Val Ala Asp
     50
                         55
Ile Leu Phe Gln Thr Ala Gln Asn Ala Gly Ile Ser Phe Asp Thr Val
                    70
Cys Gly Val Pro Tyr Thr Ala Leu Pro Leu Ala Thr Val Ile Cys Ser
Thr Asn Gln Ile Pro Met Leu Ile Xaa Arg Lys Glu Thr Lys Asp Tyr
            100
                                105
                                                    110
Gly Thr Lys Arg Leu Val Xaa Xaa Ile Leu Ile Xaa Xaa Lys Leu Phe
                            120
```

Asn His

130

<210> 806

```
<211> 35
<212> PRT
<213> Homo sapiens
<400> 806
Val Ala Asp Ile Ala Trp Trp Phe Arg Arg Ile Phe Ile Ala Val
Leu Arg Cys Asn Ser Ser Ile Ser Asp Ala Glu Ser Met Met Ser Ala
                                 25
Ile Phe His
         35
<210> 807
<211> 72
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<213> Homo sapiens
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<222> (68)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 807
Asp Trp Arg Gln Thr Ser Xaa Ser Gly Ala His Gly Arg Leu Lys Pro
                                     10
Trp Xaa Asn Pro Xaa Ala Arg Arg Asp Ala Arg Glu Asp Arg Ala Thr
             20
                                 25
Trp Lys Ser Asn Tyr Xaa Leu Lys Ile Xaa Gln Arg Ile Gly Met Ile
Ile Leu Lys Trp Val Xaa Leu Val Gly Ser Glu Tyr Xaa Met Val Gly
     50
                         55
Xaa Pro Xaa Xaa Ser Met Ala Ser
 65
                     70
<210> 808
<211> 53
<212> PRT
<213> Homo sapiens
<220>
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<222> (30)
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<400> 808
Pro Ser Leu Lys Gly Thr Lys Ala Gly Asn Asp Leu Val Ser Leu Arg
Ala Ala Arg Thr Leu Arg Pro Pro Gly Thr Lys Pro Gly Xaa Gly Ala
                                 25
             20
Thr Phe Gly Pro Gly Leu Ser Glu Arg Ala Ser Ala Gln Arg Gly Ser
                             40
Gly Gln Leu Xaa His
     50
<210> 809
<211> 70
<212> PRT
<213> Homo sapiens
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<223> Xaa equals any of the naturally occurring L-amino acids
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<222> (23)
<223> Xaa equals any of the naturally occurring L-amino acids
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<221> SITE
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<220>
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<220>

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<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (53)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 809
Ala Xaa Glu Tyr Thr Leu Arg Thr Ser Gly Leu Thr Val Arg Pro Xaa
                                    10
Thr Ser Gly Pro Gly Cys Xaa Cys Gln Gly Gly Leu Ser Asp Leu Arg
             20
Met Gly Xaa Met Glu Trp Xaa Arg Arg Asp Ala Gly Val Xaa Ala Gly
Xaa Asp Arg Ser Xaa Thr His Glu Cys Gln Val Gln Val Val Arg Val
                         55
Gly Asp Met Ser Leu Glu
 65
<210> 810
<211> 39
<212> PRT
<213> Homo sapiens
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<223> Xaa equals any of the naturally occurring L-amino acids
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<220>
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<221> SITE
<222> (39)
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<400> 810
Xaa Ile Xaa Xaa Cys Gly Phe Glu Pro Pro His Phe Leu Thr Leu Asn
Leu Xaa Met His Arg Xaa Ser Cys Pro Leu Asp Cys Lys Val Tyr Val
Gly Ile Leu Gly Thr Met Xaa
         35
<210> 811
<211> 27
<212> PRT
<213> Homo sapiens
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<222> (22)
<223> Xaa equals any of the naturally occurring L-amino acids
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<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (25)
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<400> 811
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5
                                 10
 1
Lys Lys Lys Lys Xaa Pro Xaa Xaa Gly Pro
           20
<210> 812
<211> 72
<212> PRT
<213> Homo sapiens
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<222> (21)
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Arg Arg Arg Xaa Arg Pro Ala Pro Pro Pro Gly Ala Cys Leu His Leu
                5
                                 10
Arg Leu Pro Lys Xaa Leu Gly Gln Arg Leu Asp Ala Arg His Gln Gly
Pro Val Glu Val Leu Gln Glu Glu Arg Arg Pro Arg Pro Arg Leu Pro
                          40
Arg Pro Ala Leu Ala Thr Leu Ser Ala Arg Phe Thr Asn Lys Leu Ser
    50
Asp Pro Lys Lys Lys Lys Lys
                   70
 65
<210> 813
<211> 27
<212> PRT
<213> Homo sapiens
<220>
<221> SITE
<222> (4)
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<223> Xaa equals any of the naturally occurring L-amino acids

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<220> '
<221> SITE
<222> (5)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 813
10
Lys Lys Lys Lys Lys Lys Lys Lys Lys
          20
<210> 814
<211> 23
<212> PRT
<213> Homo sapiens
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<221> SITE
<222> (23)
<223> Kaa equals any of the naturally occurring L-amino acids
10
Lys Lys Lys Lys Lys Xaa
          20
<210> 815
<211> 46
<212> PRT
<213> Homo sapiens
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<222> (19)
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<220>
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795

<223> Xaa equals any of the naturally occurring L-amino acids

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<220>
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<222> (31)
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<221> SITE
<222> (38)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (46)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 815
Phe Asp Gln Arg Thr Arg Ile Thr Arg Pro Gln Arg Arg Val Phe Xaa
Ala Ser Xaa Ser Pro Pro Lys Xaa Ile Thr Asn Cys Ile Tyr Xaa Lys
             20
                                  25
                                                      30
Ile Asn Arg Tyr Xaa Xaa Leu Asn Ile Ala Ile Gln Ile Xaa
         35
                             40
<210> 816
<211> 52
<212> PRT
<213> Homo sapiens
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<223> Xaa equals any of the naturally occurring L-amino acids
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<222> (50)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 816
Asn Ser Ala Xaa Leu Lys Gln Thr Gly Leu Lys Gly Val Thr Phe Asn
Lys Arg Met Lys Met Xaa Lys Lys Lys Lys Lys Lys Lys Lys Lys
                                 25
Lys Lys Lys Lys Lys Lys Lys Xaa Pro Gly Gly Xaa Pro Pro Pro
Pro Xaa Pro Pro
     50
<210> 817
<211> 113
<212> PRT
<213> Homo sapiens
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<222> (69)
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<223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (100) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (110) <223> Xaa equals any of the naturally occurring L-amino acids <400> 817 Xaa Ser Gly Arg Gly Gly Ser His Ser Arg Asn Leu Val Leu Phe Phe 10 5 Pro Gln Leu Gly Lys Arg His Met Ser Leu Ala Xaa Pro Ile Ala Asn 25 Pro Val Val Gly Phe Leu Ala Tyr Ser Arg Pro Ser Val Leu Pro Gly 40 Trp His Arg Pro His Arg Thr Ser Arg Val Gly Leu Ser Gly Ser Ser 50 55 Thr Ala Gly Xaa Xaa Asn Ser Arg Phe Gly Gly Cys Ser Phe Gln Ala 75 70 Gly Asp Thr Leu Gly Pro Val Val Arg Ser Pro Val Leu Arg His Leu 90 Val Trp Asn Xaa Arg Leu Ala Val Ser Ile Gly Val Gly Xaa Cys Ala 100 105 Ala <210> 818 <211> 132 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (5) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE

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Phe Phe Phe Xaa Lys Gly Thr Xaa Thr Xaa Leu Pro Phe Xaa Pro
Asn Gln Asn Gln Asn Pro Xaa Gln Ser Ile Xaa Lys Ser Lys Pro Gly
Gln Asn Gln Asn Glu Xaa Xaa Lys Gln Ser Lys Ser Ser Gln Lys Gln
Lys Pro Lys Cys Arg Tyr Arg Xaa Xaa Val Gly Asp Gln Ala Thr Leu
Pro Leu Lys Trp Ser Gly Xaa Xaa Pro Lys Thr Ser Xaa Thr Xaa Phe
Xaa Xaa Ser Gly Xaa Gln Xaa Pro Val Pro Ser Gln Xaa Xaa Ala Ala
                                     90
Xaa Leu Ile Leu Cys Gly Gly Leu Xaa Asn Ala Xaa Leu Ala Arg Cys
Ser Thr Gly Xaa Ile Ala Tyr Pro Xaa Val Leu Ser Gly Ser Xaa Ser
                           120
Leu Lys Leu Ala
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<210> 819
<211> 62
<212> PRT
<213> Homo sapiens
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<222> (54)
<223> Xaa equals any of the naturally occurring L-amino acids
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<400> 819
Asn Ser Ala Xaa Gln Thr Thr Pro Ser Leu Ser Tyr Val Phe Leu Leu
                                  10
Gln Thr Thr Arg Gln Leu Leu Lys Pro Ala Ile His Val Tyr Phe Asn
            20
                              25
                                                 30
Lys Lys Lys Lys Xaa Xaa Gly Gly Pro Pro Pro Pro
<210> 820
<211> 40
<212> PRT
<213> Homo sapiens
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<222> (27)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (38)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 820
Asp His Thr Ser Asp Thr Xaa Ala Trp Val Thr Glu Arg Asp Ser Val
                                   10
                 5
Xaa Gly Lys Glu Lys Lys Lys Lys Xaa Xaa Gly Gly Ala Pro Val
            20
                               25
Pro Asn Trp Pro Tyr Xaa Gly Ser
       35
<210> 821
<211> 64
<212> PRT
<213> Homo sapiens
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<221> SITE
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<400> 821
Ala Xaa Pro Thr Gln Gln Ser Phe Pro Gln Leu Pro Arg Arg Lys Gly
                5
                       10
Pro Ser Trp Val Trp Asp His Lys Gly Gly Asp Cys Thr Pro Leu Pro
Leu Gly Pro Gly Cys Gly Gln Arg Pro Pro Cys Val Ser Arg Val Thr
                           40
Val Pro Leu Ser Cys Asp Ala Ile Ser Val Cys Ala Trp Ser Pro Gln
    50 55
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<210> 822

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<211> 61
<212> PRT
<213> Homo sapiens
<220>
<221> SITE
<222> (23)
<223> Xaa equals any of the naturally occurring L-amino acids
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His Leu Cys Phe Lys Trp Gly Ser Pro Cys Arg Gly Phe Ile Gly His
                                     10
Trp Leu Ser Lys Cys Gln Xaa Trp Ala Gly Gly Gly Thr Glu Pro Pro
                                 25
Gln His Cys Ala Leu Val Glu Lys Ala Leu Thr Cys His Ala Pro Leu
         35
Lys Pro Pro Leu Leu Thr Cys Leu Leu His Pro Ser His
     50
                         55
<210> 823
<211> 73
<212> PRT
<213> Homo sapiens
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<221> SITE
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<222> (57)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (72)
<223> Xaa equals any of the naturally occurring L-amino acids
Thr Ala Gly Arg Trp Pro Trp Lys Ser Glu Ser Ala Lys Glu Cys Val
                                     10
  1
                  5
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PCT/US00/05881 WO 00/55173

804

Thr Thr His Leu Pro Asn Gln Leu Ala Leu Lys Met Asp Gly Ala Gly 20 25 Ala Ser Gly Pro Tyr Pro Ser Val Ala Gly Ser Arg Glu Trp Thr Gly 40 Xaa Ala Gly Ala Ala Arg Ala Arg Xaa Val Met Val Cys Val Gly Gly 50 55 Arg Arg Arg Arg Gly Cys Xaa Val 70 65 <210> 824 <211> 34 <212> PRT <213> Homo sapiens <220> <221> SITE <222> (3) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (12) <223> Xaa equals any of the naturally occurring L-amino acids <220>

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<222> (27)

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<220>

<221> SITE.

<222> (31)

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<400> 824

Pro Arg Xaa Arg Arg Gln Gln Pro His His Xaa Val Ala Asp Gly 10

Pro His Ala Gly Gly Pro Leu Pro Ala Leu Xaa Arg Arg Leu Xaa Leu 25 20

Pro Leu

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<210> 825
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<212> PRT
<213> Homo sapiens
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<223> Xaa equals any of the naturally occurring L-amino acids
<220>
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<222> (7)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (19)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 825
Pro Tyr Ser Glu Ser Xaa Xaa Asn Ser Leu Ala Val Val Leu Gln Arg
                                     10
Arg Asp Xaa Glu Asn
             20
<210> 826
<211> 56
<212> PRT
<213> Homo sapiens
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<221> SITE
<222> (48)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>
<221> SITE
<222> (56)
<223> Xaa equals any of the naturally occurring L-amino acids
<400> 826
Met Ser Glu Ala Cys Ile Val Ile Ile Ser Tyr Phe Phe Pro Leu Asp
                  5
Pro Ser His Gln Met Phe Val Asp Phe Ile Arg Ile Phe Lys Leu Pro
                                                     30
             20
                                 25
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<221> SITE

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Ala Ser Gly Phe Val Glu Leu Gly Ile Ser Val Ser Leu Ile Phe Xaa
Leu Leu Ser Cys Thr Tyr Phe Xaa
<210> 827
<211> 54
<212> PRT
<213> Homo sapiens
<220>
<221> SITE
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<221> SITE
<222> (41)
<223> Xaa equals any of the naturally occurring L-amino acids
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<400> 827
Asn Ser Lys Xaa Ile Thr Ile Lys Lys Ala Gly Thr Pro Ala Gly Thr
Gly Pro Glu Phe Pro Gly Arg Pro Thr Arg Pro Thr Ala Ala Arg Arg
             20
Arg Gln Lys Gly Thr Ala Ala Arg Xaa Arg Gln Lys Gly Ala Xaa Glu
                             40
Arg Arg Arg Gln Lys Gly
     50
<210> 828 .
<211> 78
<212> PRT
<213> Homo sapiens
<220>
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807

<222> (43) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (56) <223> Xaa equals any of the naturally occurring L-amino acids <400> 828 Leu Val Phe Thr Glu Thr Leu Arg Glu His Lys Phe Met Gly Phe Leu 5 10 Met Met Ile Leu Leu Gly Ile Met Ser Tyr Ser Leu Ser Ser Leu Met Asn Val Lys Leu His Cys Ser Gln Arg Phe Xaa Leu Leu Ser Thr Ala 40 Ile Asn His Gly His Ser Pro Xaa Asn Ile Ile Phe Phe Leu Leu Lys 55 Glu Lys Asn Gly Lys Lys Leu Gln Gly Asn Gly Asn Tyr Tyr 70 <210> 829 <211> 89 <212> PRT <213> Homo sapiens

<400> 829

Ser Ala Glu Glu Lys Lys Leu Thr Arg Ile Pro Ser Val Thr Ala Ser 1 5 10 15

Glu Gln Gly Arg Ala Gln Arg Arg Ile Pro Ala Pro Arg Arg Gly Ala
20 25 30

Gly His Val Ala Tyr Gly Arg Pro Ala Pro Arg Arg Arg Ser Trp Gly
35 40 45

Ala Gln Val Leu Leu Ile Glu Ala Gln Pro Val Asp Gly Val Arg Pro 50 60

Val Ala Ala Pro Gly Ala Pro Gly Pro Gly Leu Pro Gly Val Gly Leu
65 70 75 80

Leu Gly Asn Ala Ala Gln Ser Gly Trp

<210> 830

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<211> 43
<212> PRT
<213> Homo sapiens
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Val Pro Ser His Ser Glu Asp Ala Leu Arg Thr Leu Gln Ile Leu Leu
                                 25
Pro Tyr Ile Thr Leu Asn Ser Gly Leu Arg Xaa
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Ile Thr Val Lys Gly Gln Arg Leu Arg Ser Ala Lys Gly Gly Ala
                                 25
             20
Gln Xaa Arg Ser Thr Thr Asp Glu Ala Thr Ala Ser Ile Cys Pro Leu
                             40
Pro Val Glu Pro Tyr Arg Gln His Leu Ile Leu Thr Ala Thr Cys Asp
     50
                         55
                                             60
Asn Xaa Gln Glu Val Leu Pro Ile Leu Pro Thr Arg Ala Ala Ser Leu
                     70
                                         75
Gly Asp Leu Cys Val Pro Xaa Phe Xaa Val Cys Leu Gly Asp Arg Val
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                                105
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                                     10
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810

30 25 20 Ser Leu Leu Cys Asn Cys Trp Arg Ile Thr Ala Glu Phe Leu Ala Val 40 Leu Ser 50 <210> 833 <211> 47 <212> PRT . <213> Homo sapiens <220> <221> SITE <222> (10) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (13) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (17) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (32) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (34) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (38) <223> Xaa equals any of the naturally occurring L-amino acids <220> <221> SITE <222> (40) <223> Xaa equals any of the naturally occurring L-amino acids <400> 833

811

His Leu Lys Leu Clu Glu Arg Xaa Gln Arg Xaa Ser Gly Arg

1 5 10 15

Xaa Thr Thr Leu Gly Gly Arg Ser Thr Gly Leu Val Ile Glu Leu Xaa 20 25 30

Leu Xaa Arg Leu Leu Xaa Cys Xaa Met Asn Cys Asn Ile Cys Leu 35 40 45

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Ala Ala Arg Arg Xaa Gln Lys Gly Thr Ala Ala Arg Arg Arg Gln Lys
20 25 30

Gly Thr Ala Ala Arg Arg Arg Gln Lys Gly Thr Ala Ala Arg Arg Arg 35 40 45

Gln Lys Val Arg Leu Arg Glu Asp Asp Arg Arg Ile Arg Leu Arg Glu
50 55 60

Asp Asp Arg Glu Asn Leu Ser Ser Thr Leu Asn Leu Pro Thr Glu 65 70 75 80

Pro Ser Lys Ser Pro Cys Lys Phe Asn Cys

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                                     10
Gly Ser Leu Cys Cys Leu Tyr Cys Ile Asp Leu Xaa Tyr Arg Cys Leu
             20
                                 25
                                                     30
Phe Ile Lys Lys Lys Ile Gln Lys Xaa Lys Lys Ile Asn Lys Xaa
         35
                             40
Lys Lys Xaa
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<212> PRT
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                                     10
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                                 25
Thr Trp Phe Cys Phe Asn Lys Ser Leu Glu Lys Leu Ile Xaa Xaa
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tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca aagccgcggg 240
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agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac accctgcccc 420
cateceggga tgagetgace aagaaceagg teageetgac etgeetggte aaaggettet 480
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814 '

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cccgaaatat ctgccatctc aattag
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<213> Homo sapiens
<400> 840
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<212> DNA
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aaatatetge cateteaatt agteageaac catagteeeg eccetaaete egeceateee 120
gecectaact eegeceagtt eegeceatte teegeceeat ggetgactaa tttttttat 180
ttatgcagag gccgaggccg cctcggcctc tgagctattc cagaagtagt gaggaggctt 240
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<210> 842
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PCT/US00/05881

815

WO 00/55173

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cagttccgcc	cattctccgc	cccatggctg	actaatttt	tttatttatg	cagaggccga	180
ggccgcctcg	gcctctgagc	tattccagaa	gtagtgagga	ggctttttg	gaggcctagg	240
cttttgcaaa						256

International application No. PCT/US00/05881

A. CLASSIFICATION OF SUBJECT MATTER IPC(7): C07H 21/04; C07K 5/04, 16/00; G01N 33/53 US CL: 536/23.1; 530/300, 387.9; 436/501 According to International Patent Classification (IPC) or to both national classification and IPC							
B. FIELDS SEARCHED							
Minimum documentation searched (classification system follower	by classification symbols)						
U.S. : 536/23.1; 530/300, 387.9; 436/501							
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.							
Electronic data base consulted during the international search (na	me of data base and, where practicable, search terms used)						
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) East, GenEmbl, EST, GeneSeq, PIR-63, SwissProt, SPTREMBL, Issued patents sequence database: SEQ ID NO:1 and monoamine adj oxidase							
C. DOCUMENTS CONSIDERED TO BE RELEVANT							
Category* Citation of document, with indication, where app	propriate, of the relevant passages Relevant to claim No.						
X ZHU et al. Promoter organization and a oxidase (MOA) A and B genes. J. I Vol. 12, No. 11, pages 4437-4446, esp	Nuerosci. November 1992, 23						
1	13, 17-19						
X CHEN et al. The deduced amino acid							
	and frontal cortex monoamine oxidase B are identical. J. Neurochem. July 1993, Vol. 61, No. 1, pages 187-190, especially pages 188-190.						
GRIMSBY et al. Human monoamine o identical exon-intron organization. Pr May 1991, Vol. 88, pages 3637-3641,	oc. Natl. Acad. Sci., USA. 23						
X Further documents are listed in the continuation of Box C.							
 Special categories of cited documents: A' document defining the general state of the art which is not considered to be of particular relevance 	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention						
E earlier document published on or after the international filing date	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone						
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	 Y- document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is 						
document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than document member of the same patent family							
the priority date claimed							
Date of the actual completion of the international search OI JUNE 2000 Date of mailing of the international search report 05 JUL 2000							
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT	Authorized officer MARJORIE MORAN Authorized officer JOYCE BRIDGERS PARALEGAL SPECIALIST						
Washington, D.C. 20231	Telephone No. (703) 308-1235						
Facsimile No. (703) 305-3230	LEIGHIUH TO. (103) 300-1433 / /L/14 9						

International application No.
PCT/US00/05881

C (Continua	ation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the releva	Relevant to claim No	
X Y	BACH et al. cDNA cloning of human liver monoamine and B: Molecular basis of differences in enzymatic pro Proc. Natl. Acad. Sci., USA. July 1988, Vol. 85, pages 4938, especially pages 4935-4936.	1-16, 20-23 17-19	
Y	US 5,783,680 A (BRUNNER et al.) 21 July 1998, colur	mns 5-15.	13, 17-19
:	·		
	2		
			-

International application No. PCT/US00/05881

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)				
This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:				
ı. [Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:			
2.	Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:			
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).			
Box II	Observations where unity of invention is lacking (Continuation of item 2 of first sheet)			
This In	ternational Searching Authority found multiple inventions in this international application, as follows:			
j	Please Sec Extra Sheet.			
1.	As all required additional search fees were timely paid by the applicant, this international search report covers all searchabl claims.			
2.	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite paymer of any additional fee.			
3.	As only some of the required additional search fees were timely paid by the applicant, this international search report cover only those claims for which fees were paid, specifically claims Nos.:			
4. [No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-23, SEQ ID NO:1			
Rema	rk on Protest The additional search fees were accompanied by the applicant's protest.			
1	No protest accompanied the payment of additional search fees.			

Form PCT/ISA/210 (continuation of first sheet(1)) (July 1998)*

International application No. PCT/US00/05881

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s)1-10 and 21, drawn to isolated nucleic acid sequences, a gene, a recombinant vector and host cells comprising the sequences.

Group II, claim(s) 11-12 and 14, drawn to an isolated polypeptide and a recombinant host cell expressing the polypeptide.

Group III, claim(s) 13, drawn to an antibody.

Group IV, claim(s)15-16, drawn to a method of making a polypeptide and the polypeptide made.

Group V, claim(s) 17, drawn to a method of preventing, treating, or ameliorating a medical condition by administering a polypeptide or a polynucleotide.

Group VI, claim(s) 18, drawn to a method of diagnosis using a polynucleotide.

Group VII, claim(s) 19, drawn to a method of diagnosis using a polypeptide.

Group VIII, claim(s) 20 and 23, drawn to a method of identifying a binding partner to a polypeptide.

Group IX, claim(s) 22, drawn to a method of identifying biological activity.

In addition, each isolated nucleic acid represented by SEQ ID NO: X is a separate product, not necessarily related to any other nucleic acid represented by SEQ ID NO: X. Each polypeptide is likewise considered a separate product, not necessarily related to any other polypeptide sequence, or to any nucleotide sequence. Applicant is required to elect either ten nucleic acid sequences or one polypeptide sequence for search.

The inventions listed as Groups I-IX do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: every nucleic acid sequence claimed is not unique (SEQ ID NO: 1 is not unique, see the Search report), and therefore does not represent a special technical feature. As the nucleic acid would be the "linking" feature, and the nucleic acid is not a special technical feature, the claims do not relate to a single inventive concept. Because there is no single inventive concept, a method of use is not included with the nucleic acids of Group I.

Although unity of invention is lacking for Groups I-IX, as previously set forth, no invitation to pay for a search for extra groups has been made. However, unity of invention is also lacking with regard to sequences and applicant was invited to pay for a search for additional groups of sequences. Applicant elected only SEQ ID NO:1, therefore no extra search fees are due.